

FEE TRANSMITTAL for FY 2007

Effective 2/8/2006. Patent fees are subject to annual revision.

 Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT (\$)

1,120

Complete If Known

Application Number	Patent No. 5,703,017
Filing Date	April 13, 1994 (Issue Date: December 30, 1997)
First Named Inventor	Ernst Baumann
Examiner Name	
Art Unit	
Attorney Docket No.	AUG 6 7 2007

RECEIVED

PAYER: ACPATENTS
ATTORNEY: ACPATENTS

METHOD OF PAYMENT (check all that apply)

 Check Credit card Money Other None
Order
 Deposit Account:

Deposit Account Number

01-0025

Deposit Account Name

Abbott Laboratories

The Director is authorized to: (check all that apply)

 Charge fee(s) indicated below Credit any overpayments
 Charge any additional fee(s) during the pendency of this application
 Charge fee(s) indicated below, except for the filing fee
 to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Small Entity

Fee Code	Fee (\$)	Fee Code	Fee (\$)	Fee Description	Fee Paid
1011	300	2011	150	Utility filing fee	
1012	200	2012	100	Design filing fee	
1013	200	2013	100	Plant filing fee	
1014	300	2014	150	Reissue filing fee	
1005	200	2005	100	Provisional filing fee	

SUBTOTAL (1)

(\$0)

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

	Extra Claims	Fee from below	Fee Paid
Total Claims	-20 **	= 0	X = 0
Independent Claims	-3 **	= 0	X = 0
Multiple Dependent			= 0

Large Entity Small Entity

Fee Code	Fee (\$)	Fee Code	Fee (\$)	Fee Description
1202	50	2202	25	Claims in excess of 20
1201	200	2201	100	Independent claims in excess of 3
1203	360	2203	180	Multiple dependent claim, if not paid
1204	200	2204	100	** Reissue independent claims over original patent
1205	50	2205	25	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2)

(\$0)

** or number previously paid, if greater; For Reissues, see above

3. ADDITIONAL FEES

Large Entity Small Entity

Fee Code	Fee (\$)	Fee Code	Fee (\$)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	120	2251	60	Extension for reply within first month	
1252	450	2252	225	Extension for reply within second month	
1253	1020	2253	510	Extension for reply within third month	
1254	1,590	2254	795	Extension for reply within fourth month	
1255	2,160	2255	1080	Extension for reply within fifth month	
1401	500	2401	250	Notice of Appeal	
1402	500	2402	250	Filing a brief in support of an appeal	
1403	1000	2403	500	Request for oral hearing	
1452	500	2452	250	Petition to revive - unavoidable	
1453	1500	2453	750	Petition to revive - unintentional	
1462	400	1462	400	Petition fee under 37 CFR 1.17(f)	
1463	200	1463	200	Petition fee under 37 CFR 1.17(g)	
1464	130	1464	130	Petition fee under 37 CFR 1.17(h)	
1807	50	1807	50	Processing fee under 37 CFR 1.17 (q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	790	2809	395	Filing a submission after final rejection (37 CFR § 1.129(a))	
1810	790	2810	395	For each additional invention to be examined (37 CFR § 1.129(b))	
1801	790	2801	395	Request for Continued Examination (RCE)	

Other fee (specify) Application of Extension of Patent Term

1,120

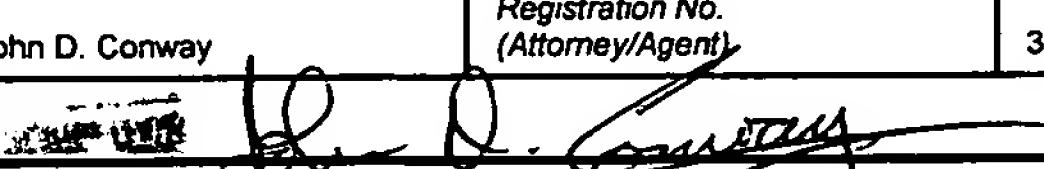
*Reduced by Basic Filing Fee Paid SUBTOTAL (3) (\$1,120)

4. SEARCH/EXAMINATION FEES

1111	500	2111	250	Utility Search Fee	
1112	100	2112	50	Design Search Fee	
1113	300	2113	150	Plant Search Fee	
1114	500	2114	250	Reissue Search Fee	
1311	200	2311	100	Utility Examination Fee	
1312	130	2312	65	Design Examination Fee	
1313	160	2313	80	Plant Examination Fee	
1314	600	2314	300	Reissue Examination Fee	

SUBTOTAL (4) (\$0)

SUBMITTED BY

Name (Print/Type)	John D. Conway	Registration No. (Attorney/Agent)	39,150	Telephone	508-688-8046
Signature				Date	August 7, 2007

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 5,703,017

Title: 3-(HET)ARYLCARBOXYLIC ACID DERIVATIVES, THEIR PREPARATION AND INTERMEDIATES FOR THEIR PREPARATION

Issue Date: 30 December 1997

Inventors: Ernst Baumann, Joachim Rheinheimer, Uwe Josef Vogelbacher, Matthias Bratz, Hans Theobald, Matthias Gerber, Karl-Otto Westphalen, Helmut Walter and Wilhelm Rademacher

Patent Owner: Abbott GmbH & Co. KG

Unit: OPLA

Attn: Mary C. Till

7 August 2007

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PATENT EXTENSION
AC PATENTS

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Office of Patent Legal Administration
Room MDW 7D55
600 Dulany Street (Madison Building)
Alexandria, VA 22314

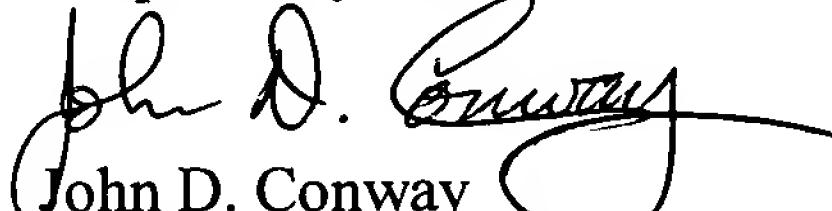
APPLICATION FOR PATENT TERM EXTENSION UNDER 35 U.S.C. §156

In support of the Application for Patent Term Extension of U.S. Patent No. 5,703,017, Applicant submits the following:

1. PTE Application (being submitted as one original and two additional copies thereof)
2. Exhibits A-L
3. Duplicate Fee Transmittal Sheet

Applicant certifies that the two additional copies are identical to the original being submitted.

Respectfully submitted,


John D. Conway

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Attorney for Applicant
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Fax: 508-688-8110

Enclosure

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 5,703,017

Title: 3-(HET)ARYLCARBOXYLIC ACID DERIVATIVES, THEIR PREPARATION AND INTERMEDIATES FOR THEIR PREPARATION

Issue Date: 30 December 1997

Inventors: Ernst Baumann, Joachim Rheinheimer, Uwe Josef Vogelbacher, Matthias Bratz, Hans Theobald, Matthias Gerber, Karl-Otto Westphalen, Helmut Walter and Wilhelm Rademacher

Patent Owner: Abbott GmbH & Co. KG

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Attn: Mary C. Till

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Alexandria, VA 22314

APPLICATION FOR PATENT TERM EXTENSION UNDER 35 U.S.C. §156

Abbott GmbH & Co. KG (“Applicant”) of Max-Planck-Ring 3, 65205 Wiesbaden, Germany, submits this application for extension of patent term of U.S. Patent No. 5,703,017 (“U.S. ‘017”) under 35 U.S.C. §156. The relevant facts establishing the authority of Applicant to file this application for extension of patent term in accordance with 37 C.F.R. §1.730 are set forth below:

- On 28 September 1995, Ernst Baumann, Joachim Rheinheimer, Uwe Josef Vogelbacher, Matthias Bratz, Hans Theobald, Matthias Gerber, Karl-Otto Westphalen, Helmut Walter and Wilhelm Rademacher (inventors of the subject matter claimed in U.S. ‘017) assigned to BASF Aktiengesellschaft all right, title and interest in their invention. This assignment was recorded in the United States Patent and Trademark Office on 19 October 1995 at Reel 008091, Frame 0666. A copy of this assignment is attached as Exhibit A-1.

- On 17 October 2006, BASF Aktiengesellschaft assigned to Abbott GmbH & Co. KG all right, title and interest in U.S. '017. This assignment was recorded in the United States Patent and Trademark Office on 30 October 2006 at Reel 018454, Frame 0430. A copy of this assignment is attached as Exhibit A-5.
- The Investigational New Drug application (“INDA”) for ambrisentan was originally filed by Myogen, Inc. Effective on 17 November 2006, Myogen, Inc. was acquired by Gilead Sciences, Inc. (“Gilead”) and became a wholly owned subsidiary known as Gilead Colorado, Inc. A copy of the New Drug application (“NDA”) submission letter indicating this fact is attached as Exhibit B.
- Gilead is the exclusive licensee to U.S. '017.
- Gilead is the sponsor of the drug product, LETAIRIST™ (ambrisentan), for which the FDA granted regulatory approval and which forms the basis of this patent term extension. A copy of the approval letter is attached as Exhibit C.
- Applicant is authorized by Gilead to rely on its activities and the activities of its predecessor, Myogen, Inc., before the Food and Drug Administration (“FDA”) for regulatory review activities. Gilead has executed a statement authorizing reliance by Applicant on such activities of Gilead. A copy of this statement is attached as Exhibit D.

The following information is submitted in accordance with 35 U.S.C. §156(d) and 37 C.F.R. §§1.740 to 1.741. The formal requirements of 37 C.F.R. §1.740 are specifically set out below.

1. Identification of Approved Product [37 C.F.R. §1.740(a)(1)]

The approved product is LETAIRIST™ (ambrisentan) 5 and 10 mg tablets for the treatment of pulmonary arterial hypertension (WHO Group 1) in patients with WHO class II or III symptoms to improve exercise capacity and delay clinical worsening. See the approved label for LETAIRIST™ tablets provided as Exhibit E. Ambrisentan is the active ingredient in LETAIRIST™ tablets. Ambrisentan is further identified as follows:

A. Chemical Name

The chemical name for ambrisentan is (+)-(2S)-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic acid.

The CAS registry number for ambrisentan is 177036-94-1.

B. Generic Name

The generic name of the active ingredient in LETAIRIST™ tablets is ambrisentan. Ambrisentan is the U.S. Adopted Name (USAN) and International Nonproprietary Name (INN) for this compound.

C. Molecular Formula

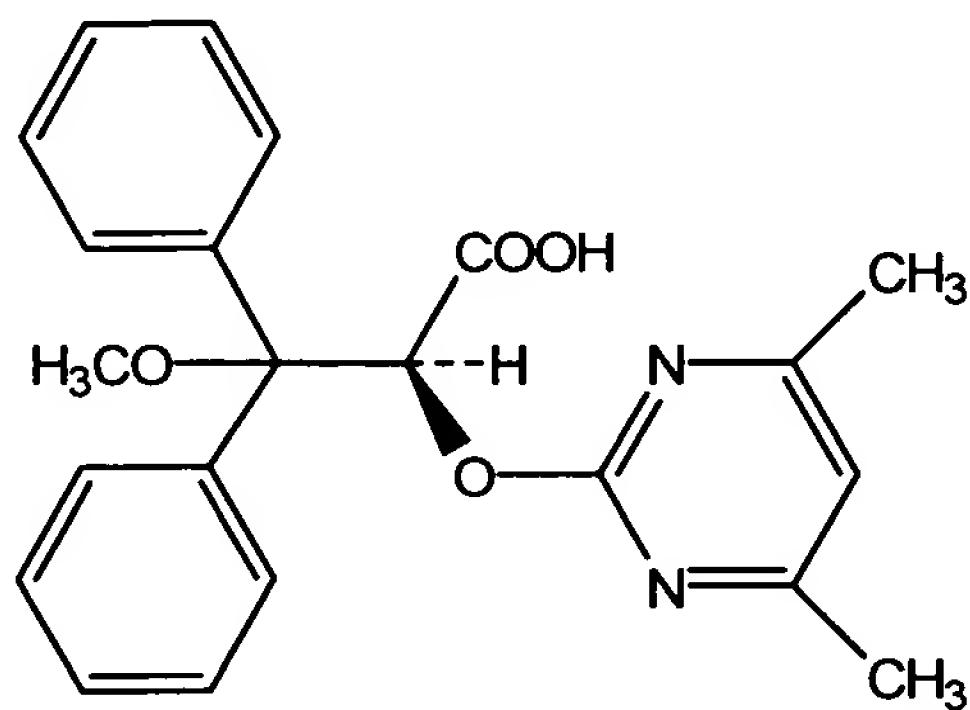
The molecular formula of ambrisentan is C₂₂H₂₂N₂O₄.

D. Molecular Weight

The molecular weight of ambrisentan is 378.42.

E. Structural Formula

The structural formula of ambrisentan is:



F. Product Ingredients

Ambrisentan is the active ingredient in LETAIRIS™ tablets, as provided in the approved label text attached as Exhibit E. As provided in Exhibit E, LETAIRIS™ tablets further contain the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. As further provided in Exhibit E, LETAIRIS™ tablets have a film coating containing FD&C Red #40 aluminum lake, lecithin, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

2. **Federal Statute under which Regulatory Review Occurred [37 C.F.R. §1.740(a)(2)]**

The approved product, LETAIRIS™ tablets, was subject to regulatory review under Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act (“FFDCA”), 21 U.S.C. §355(b)(1), as amended.

3. Date of Permission for Commercial Marketing [37 C.F.R. §1.740(a)(3)]

LETAIRIST™ product was approved by the FDA for commercial marketing pursuant to Section 505(b)(1) of the FFDCA on 15 June 2007. A copy of the letter from the FDA to Gilead, dated 15 June 2007, setting forth the approval of the product is attached as Exhibit C.

4. Identification of Active Ingredient and Certifications [37 C.F.R. §1.740(a)(4)]

- (a) The active ingredient of LETAIRIST™ is ambrisentan, (+)-(2S)-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic acid, having the structure depicted in Section 1 above.
- (b) Ambrisentan has not been approved for commercial marketing or use under the FFDCA, the Public Health Service Act, or the Virus-Serum-Toxin Act, prior to the approval granted on 15 June 2007.
- (c) The use for which the product is approved is as follows: “LETAIRIST™ is indicated for the treatment of pulmonary arterial hypertension (WHO Group 1) in patients with WHO class II or III symptoms to improve exercise capacity and delay clinical worsening.” See the approved label for LETAIRIST™ tablets provided as Exhibit E.

5. Statement of Timely Filing [37 C.F.R. §1.740(a)(5)]

The present application for extension of patent term is being submitted within the sixty-day period permitted for submission under 37 C.F.R. §1.720(f). The FDA approved commercial marketing and use of the approved product, LETAIRIST™ tablets, on 15 June 2007. The sixty-day submission period ends on 13 August 2007. As demonstrated by the signed Certificate of Hand-Delivery, this application for extension of patent term is timely submitted.

6. Identification of Patent for which Extension is Sought [37 C.F.R. §1.740(a)(6)]

U.S. Patent No: 5,703,017

Title: 3-(HET)ARYLCARBOXYLIC ACID DERIVATIVES,
THEIR PREPARATION AND INTERMEDIATES
FOR THEIR PREPARATION

Issue Date: 30 December 1997

Expiration Date: 30 December 2014

Application No.: 08/537,843

Application Filing Date: 13 April 1994 (§371 Date: 19 October 1995)

Inventors: Ernst Baumann, Joachim Rheinheimer, Uwe Josef
Vogelbacher, Matthias Bratz, Hans Theobald, Matthias
Gerber, Karl-Otto Westphalen, Helmut Walter and
Wilhelm Rademacher

Patent Owner: Abbott GmbH & Co. KG

7. Patent Copy [37 C.F.R. §1.740(a)(7)]

A copy of U.S. '017, the patent for which extension is being requested, is attached as Exhibit F. This copy contains the entire specification (including claims). There are no drawings in U.S. '017.

8. Disclaimer and Post-Issuance Activity Statement [37 C.F.R. §1.740(a)(8)]

(a) No Disclaimer has been submitted in U.S. '017.

(b) A request for Certificate of Correction was filed on 14 January 1998. The Certificate was signed and sealed on 3 March 1998. A copy of the request for Certificate of Correction and the signed and sealed Certificate dated 3 March 1998 is attached as Exhibit G-1.

- (c) A request for Certificate of Correction was filed on 3 August 2007 and is therefore pending. A copy of the request for Certificate of Correction is attached as Exhibit G-2.
- (d) U.S.‘017 has not been subject to a Reexamination Proceeding.
- (e) The first and second maintenance fees for U.S.‘017 were paid on 29 May 2001 and 27 May 2005, respectively. A copy of the maintenance fee statement showing timely payment of all necessary maintenance fees is attached as Exhibit G-3.

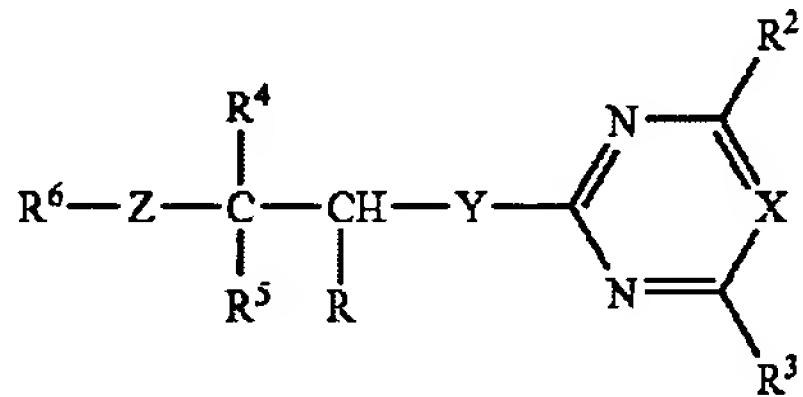
9. Statement Showing How the Claims of the Patent Cover the Approved Product
[37 C.F.R. §1.740(a)(9)]

The statements in this section are provided solely to comply with the requirements of 37 C.F.R. § 1.740(a)(9). These comments are not an assertion or an admission by the applicant as to the scope of the listed claims, or as to whether or how any of the listed claims would be infringed, literally or under the doctrine of equivalents, by the manufacture, use, sale, offer for sale or the importation of any product.

U.S. '017 has compound-per-se claims and claims to methods of making compounds related to the approved product. Each applicable patent claim is set forth below (as corrected in the Certificate of Correction signed and sealed on 3 March 1998 and the request for Certificate of Correction pending as of 3 August 2007) together with a showing of the manner in which each applicable patent claim reads on the approved product. The elements of the claims which embrace LETAIRIS™ product are shown in bold for convenience.

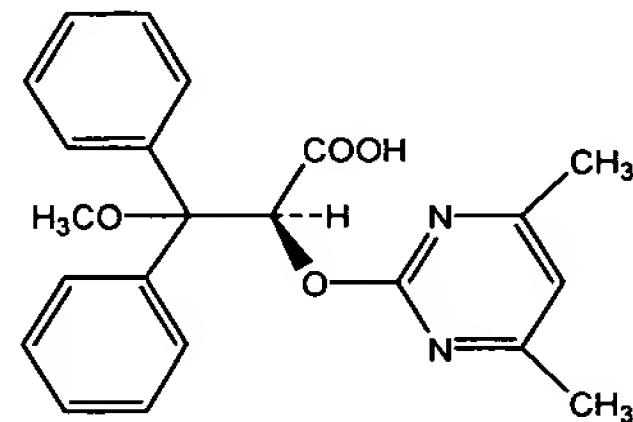
Claim 1

A 3-(het)arylcarboxylic acid derivative of the formula I



where R is formyl, CO₂H or a radical hydrolyzable to COOH and

Ambrisentan



R is carboxyl (COOH, which is the same as CO₂H)

R₂ is halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy or C₁-C₄-alkylthio;

R² is methyl (CH₃), which is a C₁ alkyl group

X is nitrogen or CR¹⁴, where R¹⁴ is hydrogen or, together with R³, forms a 3-membered or 4-membered alkylene or alkenylene chain, in each of which a methylene group is replaced by oxygen;

X is CH (where R¹⁴ is hydrogen)

R³ is halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy or C₁-C₄-alkylthio or R³ is linked to R¹⁴ as stated above to form a 5-membered or 6-membered ring;

R³ is methyl (CH₃), which is a C₁ alkyl group

R^4 is phenyl or naphthyl which may be substituted by one or more, in particular one to three, of the following radicals: halogen, nitro, cyano, hydroxyl, mercapto, amino, C_1 - C_4 -alkyl, C_1 - C_4 -haloalkyl, C_1 - C_4 -alkoxy, C_1 - C_4 -haloalkoxy, C_1 - C_4 -alkylthio, C_1 - C_4 -alkylamino, di- C_1 - C_4 -alkylamino, C_1 - C_4 -alkylcarbonyl or C_1 - C_4 -alkoxycarbonyl;

a five-membered or six-membered heteroaromatic structure which contains one to three nitrogen atoms and/or one sulfur or oxygen atom and may carry one or more of the following radicals: halogen, nitro, cyano, hydroxyl, mercapto, amino, C_1 - C_4 -alkyl, C_1 - C_4 -haloalkyl, C_1 - C_4 -alkoxy, C_1 - C_4 -haloalkoxy, C_1 - C_4 -alkylthio, C_1 - C_4 -alkylamino, C_1 - C_4 -dialkylamino, C_1 - C_4 -alkylcarbonyl, C_1 - C_4 -alkoxycarbonyl or phenyl;

R^5 is hydrogen, C_1 - C_4 -alkyl, C_3 - C_6 -alkenyl, C_3 - C_6 -alkynyl, C_3 - C_8 -cycloalkyl, C_1 - C_4 -haloalkyl, C_1 - C_4 -alkoxyalkyl, C_1 - C_4 -alkylthioalkyl or phenyl;

R^6 is C_1 - C_8 -alkyl, C_3 - C_6 -alkenyl, C_3 - C_6 -alkynyl or C_3 - C_8 -cycloalkyl, it being possible for these radicals to be mono- or polysubstituted in each case by: halogen, nitro, cyano, C_1 - C_4 -alkoxy, C_3 - C_6 -alkenyloxy, C_3 - C_6 -alkynyloxy, C_1 - C_4 -alkylthio, C_1 - C_4 -haloalkoxy, C_1 - C_4 -alkylcarbonyl, C_1 - C_4 -alkoxycarbonyl, C_1 - C_4 -alkylamino, di- C_1 - C_4 -alkylamino, phenyl or phenyl or phenoxy which is mono- or polysubstituted, for example mono- to trisubstituted, by halogen, nitro, cyano, C_1 - C_4 -alkyl, C_1 - C_4 -haloalkyl, C_1 - C_4 -alkoxy, C_1 - C_4 -haloalkoxy or C_1 - C_4 -alkylthio;

Y is sulfur or oxygen or a single bond;

R^4 is phenyl, with no substitutions

R^5 is phenyl

R^6 is methyl (CH_3), which is a C_1 alkyl group, with no substitutions

Z is sulfur or oxygen.

Y is oxygen

Z is oxygen

with the proviso that R^6 is not unsubstituted C_1 - C_4 -alkyl when

R^4 is unsubstituted phenyl, **Z** is oxygen and simultaneously R^5 is methyl or hydrogen.

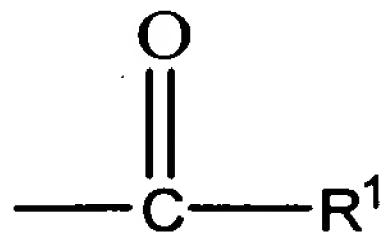
R^5 is not methyl or hydrogen

Claim 1 embraces the active ingredient of the approved product, LETAIRISTM tablets. LETAIRISTM tablets contain ambrisentan, (+)-(2S)-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3-

methoxy-3,3-diphenylpropanoic acid, which as recited above is a 3-(het)arylcarboxylic acid derivative of formula I.

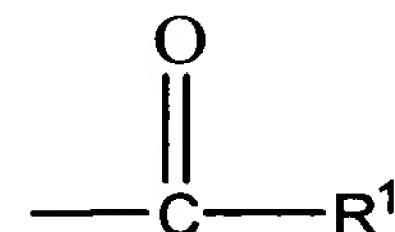
Claim 2

A 3-(het)arylcarboxylic acid derivative of the general formula I as claimed in claim 1, where **R** is



Ambrisentan

R is



where **R**¹ has the following meanings: . . .

R¹ is OH (OR¹⁰ where R¹⁰ is hydrogen)

or a radical OR¹⁰, where R¹⁰ is:

i) hydrogen, . . .

Claim 2 embraces the active ingredient of the approved product, LETAIRIS™ tablets. LETAIRIS™ tablets contain ambrisentan, (+)-(2S)-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic acid, which as recited in Claim 1 is a 3-(het)arylcarboxylic acid derivative of formula I. Claim 2 is dependent on Claim 1, therefore Claim 2 incorporates by reference all of the moieties for each of the respective substituents.

Claim 3

A 3-arylcarboxylic acid derivative of the formula I as claimed in claim 1, in which **R**⁴ is phenyl which may be substituted as stated in claim 1, and the remaining substituents have the meanings stated in claim 1.

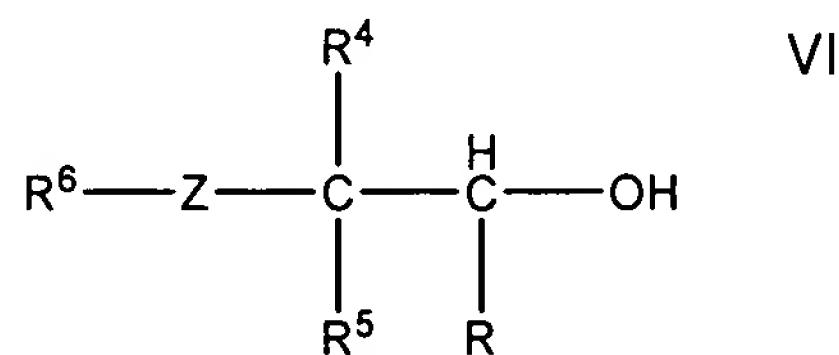
Ambrisentan

R⁴ is phenyl, with no substitutions

Claim 3 embraces the active ingredient of the approved product, LETAIRIS™ tablets. LETAIRIS™ tablets contain ambrisentan, (+)-(2S)-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic acid, which as recited in Claim 1 is a 3-(het)arylcarboxylic acid derivative of formula I. Claim 3 is dependent on Claim 1, therefore Claim 3 incorporates by reference all of the moieties for each of the respective substituents.

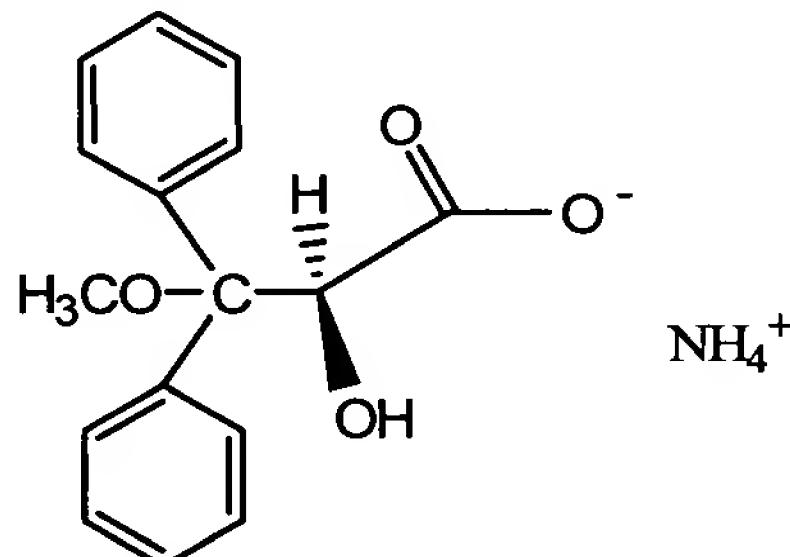
Claim 13

A process for the preparation of 3-(het)arylcarboxylic acid derivatives of the formula I as claimed in claim 1, where Y* is oxygen wherein the 3-het(aryl)carboxylic acid derivative of the formula VI



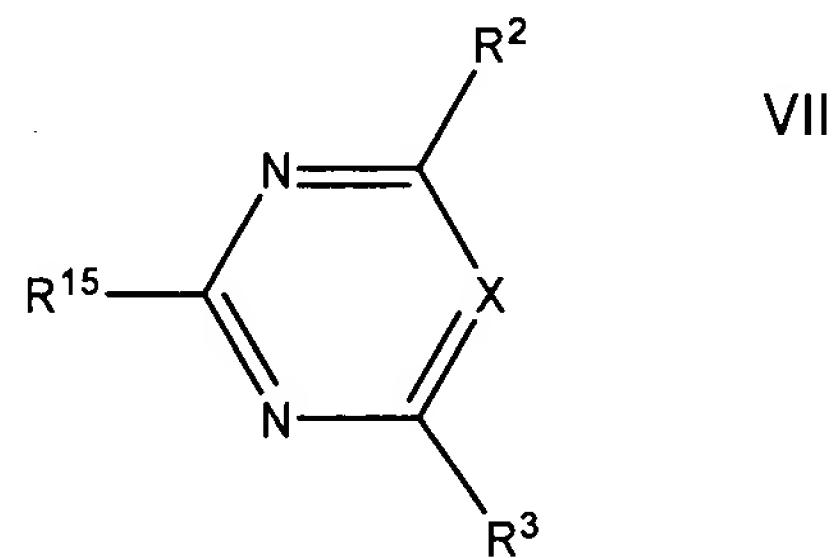
Ambrisentan

Ambrisentan is a 3-(het)arylcarboxylic acid derivative of the formula I where Y is oxygen;



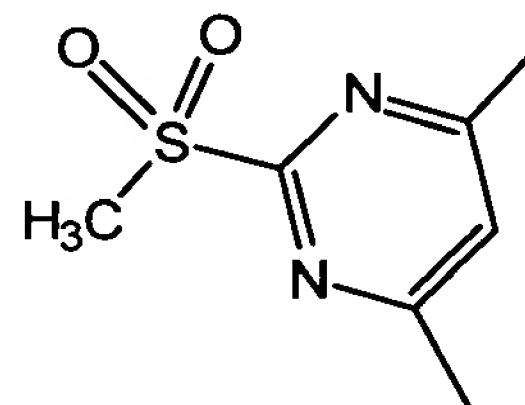
where the substituents have the meanings stated in claim 1,

is reacted with a pyrimidyl or triazinyl derivative of the formula VII



where R^{15} is halogen or $R^{16}\text{SO}_2^-$ and R^{16} is $C_1\text{-}C_4$ -alkyl, $C_1\text{-}C_4$ -haloalkyl or phenyl, in an **inert solvent** in the **presence of a base**.

* Certificate of Correction is pending.



R^{15} is $R^{16}\text{SO}_2^-$;

R^{16} is $C_1\text{-}C_4$ -alkyl (CH_3); therefore R^{15} is CH_3SO_2^- ;

inert solvent in the presence of a base is:

LiNH_2 / DMF
 H_2O / Isopropyl Acetate /
 $\text{H}_2\text{SO}_4/\text{NaOH}$

Claim 13 embraces a process for preparing the active ingredient, ambrisentan, of the approved product, LETAIRIS™ tablets.

Therefore, as demonstrated above, Claims 1, 2, 3 and 13 of U.S. '017 read on the approved product, LETAIRIS™ tablets.

10. Statement of Relevant Dates to Determine the Regulatory Review Period
[37 C.F.R. §1.740(a)(10)]

The relevant dates and information pursuant to 35 U.S.C. §156(g), in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period, are as follows:

(a) *Patent Issue Date*

U.S. '017 was issued on **30 December 1997**.

(b) *IND Effective Date [§ 1.740(a)(10)(i)(A)]*

The IND for the approved product, LETAIRIS™ tablets, was submitted to the FDA on 3 June 2002. A copy of the letter transmitting the IND to the FDA is attached as Exhibit H. The FDA accorded the IND a date of receipt of 4 June 2002, and the IND was assigned number 64,915 (“IND 64,915”). A copy of the letter from the FDA acknowledging receipt of IND 64,915 is attached as Exhibit I. Accordingly, IND 64,915 became effective on **4 July 2002**.

(c) *NDA Submission Date [§ 1.740(a)(10)(i)(B)]*

The NDA for the approved product, LETAIRIS™ tablets, was submitted to the FDA on 13 December 2006. A copy of the letter transmitting the NDA to the FDA is attached as Exhibit B. The FDA accorded the NDA a date of receipt of 18 December 2006, and the NDA was assigned number 22-081 (“NDA 22-081”). A copy of the letter from the FDA acknowledging receipt of NDA 22-081 is attached as Exhibit J. Accordingly, NDA 22-081 became effective on **18 December 2006**.

(d) *NDA Approval Date [§ 1.740(a)(10)(i)(C)]*

NDA 22-081 was approved by the FDA on **15 June 2007**. A copy of the approval letter from the FDA to Gilead is attached as Exhibit C.

**11. Brief Description of Activities Undertaken During the Regulatory Review Period
[37 C.F.R. §1.740(a)(11)]**

A description of significant activities undertaken by the marketing applicant, Gilead through Myogen, Inc. (now Gilead Colorado, Inc. a wholly owned subsidiary of Gilead), during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities are set forth in Exhibit K. Exhibit K is divided into two parts as follows: (K-1) IND 64,915 Chronology and (K-2) NDA 22-081 Chronology.

12. Opinion of Eligibility for Extension [37 C.F.R. §1.740(a)(12)]

In the opinion of Applicant, U.S.‘017 is eligible for patent term extension under the provisions of 35 U.S.C. §156. Specifically, Applicant believes that the requirements of 35 U.S.C. §156 for an extension of patent term are satisfied as follows:

(1) Patent with Eligible Subject Matter [35 U.S.C. §156(a)]

The patent has claims which embrace the active ingredient of LETAIRIST™ tablets.

(2) Non-expiration of Patent Term [35 U.S.C. §156(a)(1)]

The term of U.S.‘017 expires on 30 December 2014, based on a term that is 17 years from the issue date of the patent. Therefore, this application has been submitted before the expiration of the patent term.

(3) No Prior Patent Term Extension [35 U.S.C. §156(a)(2)]

The term of U.S.‘017 has never been extended.

(4) Owner or Agent [35 U.S.C. §156(a)(3)]

The present application for extension is submitted by the owner of record, Abbott GmbH & Co. KG in accordance with the requirements of 35 U.S.C. §156(d).

(5) Regulatory Review [35 U.S.C. §156(a)(4)]

The approved product was subject to a regulatory review period under Section 505(b)(1) of the FFDCA before its commercial marketing or use (see Exhibits B and H).

(6) First Marketing Approval [35 U.S.C. §156(a)(5)(A)]

The permission for commercial marketing of LETAIRIST™ tablets is the first permitted commercial marketing of ambrisentan.

(7) No Extension of Other Patent [35 U.S.C. §156(c)(4)]

No other patent has been extended for the same regulatory review period for the approved product, LETAIRIS™ tablets.

STATEMENT AS TO LENGTH OF EXTENSION CLAIMED

The extension period of U.S. '017, as calculated below, is 995 days from the original patent term (30 December 2014) to 20 September 2017.

Regulatory review period [§1.775(c)]

IND phase [§1.775(c)(1)]

The number of days in the period beginning on the date an exemption under FDCA §505(i) became effective for the approved product (4 July 2002) and ending on the date an NDA was initially submitted under FDCA §505 (18 December 2006) 1629 days

NDA phase [§ 1.775(c)(2)]

The number of days in the period beginning on the date the application was initially submitted for the approved product under FDCA §505 (18 December 2006) and ending on the date the NDA was approved (15 June 2007) 180 days

Total regulatory review period

1809 days

Subtractions and limitations [§1.775(d)]

Reduction for regulatory review before patent grant [§1.775(d)(1)(i)]

The number of days in the periods of §1.775(c)(1) (IND phase) and (c)(2) (NDA phase) on or before the date the patent issued (30 December 1997) 0 days

Reduction for lack of due diligence [§1.775(d)(1)(ii)]

The number of days in the periods of §1.775(c)(1) (IND phase) and (c)(2) (NDA phase) during which the applicant did not act with due diligence 0 days

Net subtraction

One-half the number of days remaining in the period of §1.775 (c)(1) (IND phase) after the reductions above 814 days

Net preliminary term extension [§1.775(d)(1)]

995 days

Fourteen Year Comparison [§1.775(d)(2)-(4)]

The new expiration date of U.S. '017 with the 995 day extension determined above is 20 September 2017, which is earlier than 15 June 2021, fourteen years from the approval date of NDA 22-081 (15 June 2007).

Five Year Comparison [§1.775(d)(5)]

The 995 day extension calculated above does not exceed five years.

Accordingly, it is respectfully requested that the term of U.S. '017 be extended 995 days from the original patent term (30 December 2014) to: 20 September 2017.

13. Duty of Disclosure [37 C.F.R. §1.740(a)(13)]

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and Secretary of Health and Human Services any information that is material to the determination of entitlement to the extension sought, particularly as that duty is defined in 37 C.F.R. §1.765.

Applicant advises that it is concurrently filing applications under 35 U.S.C. §156 and 37 C.F.R. §1.140, based on the Regulatory Review period for LETAIRIS™ product, to extend terms of following patents:

- U.S. Patent No. 5,703,017;
- U.S. Patent No. 5,840,722;
- U.S. Patent No. 5,932,730; and
- U.S. Patent No. 7,109,205.

Applicant will, during co-pendency of these four applications, elect one of the four applications to proceed to grant, and will withdraw the remaining three pending applications.

14. Fee Charge [37 C.F.R. §1.740(a)(14)]

The Commissioner of Patents and Trademarks is authorized to charge the prescribed \$1,120.00 fee set forth in 37 C.F.R. §1.20(j) for receiving and acting upon this application for extension of patent term, together with any additional fees that may be required during the entire pendency of this application for extension of patent term, to Deposit Account No. 01-0025. A Fee Transmittal (PTO/SB/17) expressly authorizing the charging of fees to Deposit Account No. 01-0025 in this matter is being submitted in duplicate with the pending application for extension of patent term.

15. Correspondence Address [37 C.F.R. §1.740(a)(15)]

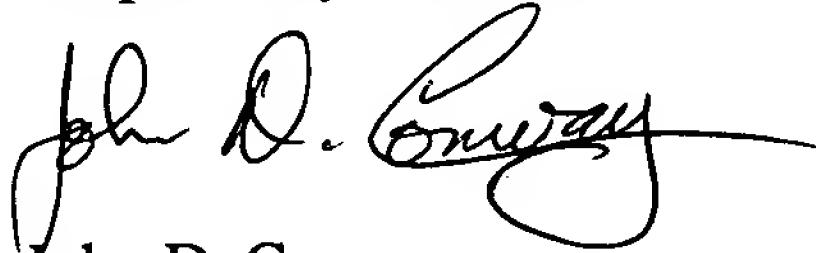
Please direct all inquiries and correspondence relating to the application for patent term extension to:

Martin L. Katz
Registration No. 25,011
Wood, Phillips, Katz, Clark & Mortimer
Citigroup Center, Suite 3800
500 West Madison Street
Chicago, IL 60661-2511

Certification under 37 C.F.R. §1.740(b)

The present application for extension of patent term for U.S. '017 is being submitted as one original and two additional copies thereof.

Respectfully submitted,

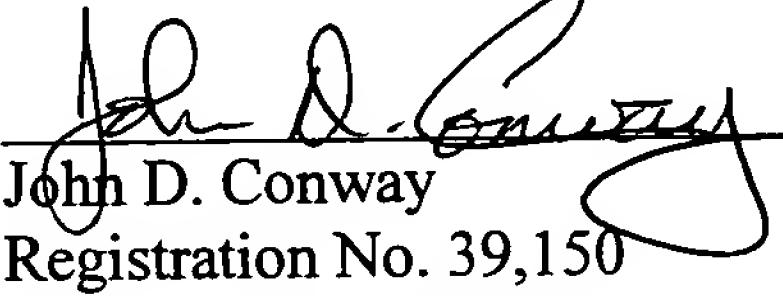


John D. Conway
Registration No. 39,150
Attorney for Applicant
Abbott Bioresearch Center
100 Research Drive
Worcester, MA 01605
Tel.: 508-688-8046
Fax: 508-688-8110

Date: 7 August 2007

CERTIFICATE OF HAND DELIVERY

The undersigned certifies that one original and two duplicate copies of this APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156 (including all Exhibits and supporting papers) are being hand-delivered this 7th day of August 2007, to "Attention: Mary C. Till, Office of Patent Legal Administration, Room MDW 7D55, 600 Dulany Street (Madison Building), Alexandria, VA 22314", United States Patent and Trademark Office.


John D. Conway
Registration No. 39,150
Attorney for Applicant
Abbott Bioresearch Center
100 Research Drive
Worcester, MA 01605
Tel.: 508-688-8046
Fax: 508-688-8110

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 5,703,017

Title: 3-(HET)ARYLCARBOXYLIC ACID DERIVATIVES, THEIR PREPARATION AND INTERMEDIATES FOR THEIR PREPARATION

Issue Date: 30 December 1997

Inventors: Ernst Baumann, Joachim Rheinheimer, Uwe Josef Vogelbacher, Matthias Bratz, Hans Theobald, Matthias Gerber, Karl-Otto Westphalen, Helmut Walter and Wilhelm Rademacher

Patent Owner: Abbott GmbH & Co. KG

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156
EXHIBIT LIST

Exhibit A: Chain of Title/Ownership Recordation

- A-1: Assignment #1
- A-2: Security Agreement
- A-3: Release of Security Interest #1
- A-4: Release of Security Interest #2
- A-5: Assignment #2

Exhibit B: Copy of letter transmitting NDA 22-081 to the FDA

Exhibit C: FDA approval letter of NDA 22-081 to Gilead Sciences, Inc.

Exhibit D: Statement of Reliance

Exhibit E: Approved label for LETAIRIST™ tablets

Exhibit F: Copy of US Patent No. 5,703,017

Exhibit G: Post-Issuance Activity Documents

- G-1: Copy of request for Certificate of Correction filed on 14 January 1998 and the signed and sealed Certificate dated 3 March 1998
- G-2: Copy of pending request for Certificate of Correction filed on 3 August 2007.
- G-3: Copy of maintenance fee statement

Exhibit H: Copy of letter transmitting IND 64,915 to the FDA

Exhibit I: Copy of letter from the FDA acknowledging receipt of IND 64,915

Exhibit J: Copy of letter from the FDA acknowledging receipt of NDA 22-081

Exhibit K: Description of significant activities

K-1 IND 64,915 Chronology

K-2 NDA 22-081 Chronology

Exhibit L: Calculation of Length of Patent Term Extension for a Human Drug Product

EXHIBIT

A

US Patent 5,703,017

HDP Reference 8493-500058

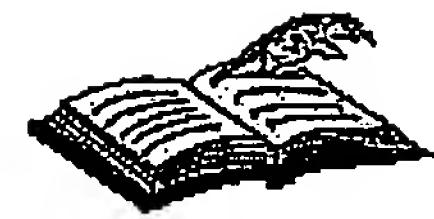
Chain of Title/Ownership Recordation

1. 008091/0666 4 Pages
Assignment
Inventors to BASF Aktiengesellschaft
2. 013616/0001 6 Pages
Security Agreement
Myogen, Inc. to GATX Ventures, Inc. and Silicon Valley Bank
3. 017480/0281 6 Pages
Release of Security Interest
Silicon Valley Bank to Myogen, Inc.
4. 017025/0877 5 Pages
Release of Security Interest
GATX Ventures, Inc. and Silicon Valley Bank to Myogen, Inc.
5. 018454/0430 4 Pages
Assignment
BASF Aktiengesellschaft to Abbott GmbH & Co. KG



United States Patent and Trademark Office

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Assignments on the Web > Patent Query

Patent Assignment Abstract of Title

NOTE: Results display only for issued patents and published applications.
For pending or abandoned applications please consult USPTO staff.

Total Assignments: 5

Patent #: 5703017 Issue Dt: 12/30/1997 Application #: 08537843 Filing Dt: 10/19/1995

Inventors: ERNST BAUMANN, JOACHIM RHEINHEIMER, UWE J. VOGELBACHER, MATTHIAS BRATZ, HANS THEOBALD et al

Title: 3-(HET) ARYLCARBOXYLIC ACID DERIVATIVES, THEIR PREPARATION AND INTERMEDIATES FOR THEIR PREPARATION

Assignment: 1

Reel/Frame: 008091/0666 Recorded: 10/19/1995 Pages: 4

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignors: BAUMANN, ERNST	Exec Dt: 09/28/1995
RHEINHEIMER, JOACHIM	Exec Dt: 09/28/1995
VOGELBACHER, UWE JOSEE	Exec Dt: 09/28/1995
BRATZ, MATTHIAS	Exec Dt: 09/28/1995
THEOBALD, HANS	Exec Dt: 09/28/1995
GERBER, MATTHIAS	Exec Dt: 09/28/1995
WESTPHALEN, KARL-OTTO	Exec Dt: 09/28/1995
WALTER, HELMUT	Exec Dt: 09/28/1995
RADEMACHER, WILHELM	Exec Dt: 09/28/1995

Assignee: BASF AKTIENGESELLSCHAFT
67056 LUDWIGSHAFEN, GERMANY

Correspondent: KEIL & WEINKAUF
HERBERT B. KEIL
1101 CONNECTICUT AVE., N.W.
WASHINGTON, D.C. 20036

Assignment: 2

Reel/Frame: 013616/0001 Recorded: 01/06/2003 Pages: 6

Conveyance: SECURITY AGREEMENT

Assignor: MYOGEN, INC.	Exec Dt: 12/06/2002
Assignees: GATX VENTURES, INC.	
3687 MT. DIABLO BLVD., SUITE 200	
LAFAYETTE, CALIFORNIA 94549	
SILICON VALLEY BANK	
4410 ARAPAHOE, SUITE 200	
BOULDER, COLORADO 80303	

Correspondent: GATX VENTURES, INC.
JOHN C. BOMBARA
ATTN: LEGAL DEPARTMENT
16 MUNSON ROAD, 5TH FLOOR
FARMINGTON, CONNECTICUT 06032

Assignment: 3

Reel/Frame: 017480/0281 Recorded: 01/23/2006 Pages: 6

Conveyance: RELEASE BY SECURED PARTY (SEE DOCUMENT FOR DETAILS).

Assignor: SILICON VALLEY BANK

Exec Dt: 01/11/2006

Assignee: MYOGEN, INC.

7575 W 103RD AVE., SUITE 102
WESTMINSTER, COLORADO 80021

Correspondent: SILICON VALLEY BANK

LOAN COLLATERAL HF154
3003 TASMAN DRIVE
SANTA CLARA, CA 95054

Assignment: 4

Reel/Frame: 017025/0877

Recorded: 01/18/2006

Pages: 5

Conveyance: RELEASE BY SECURED PARTY (SEE DOCUMENT FOR DETAILS).

Assignor: GATX VENTURES, INC. AND SILICON VALLEY BANK

Exec Dt: 01/13/2006

Assignee: MYOGEN, INC.

7575 WEST 103RD AVENUE, #102
WESTMINSTER, COLORADO 80021

Correspondent: BRAD SCHOENFELD

1675 BROADWAY, SUITE 750
DENVER, CO 80202

Assignment: 5

Reel/Frame: 018454/0430

Recorded: 10/30/2006

Pages: 4

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignor: BASF AKTIENGESELLSCHAFT

Exec Dt: 10/17/2006

Assignee: ABBOTT GMBH & CO, KG

MAX-PLANCK-RING 2
WIESBADEN, GERMANY 65025

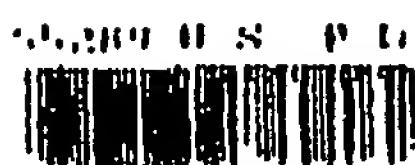
Correspondent: GAYLE B. O'BRIEN

ABBOTT BIORESEARCH CENTER
100 RESEARCH DRIVE
WORCESTER, MA 01605-4314

Search Results as of: 07/17/2007 05:45 PM

If you have any comments or questions concerning the data displayed, contact PRD / Assignments at 571-272-3350. v.2.0.1
Web interface last modified: April 20, 2007 v.2.0.1

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07/16/96

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08/537843
62 Rec'd PG/C/PC 19 OCT 1995

10-28-1995

10-19-95
08/537843

To the Honorable Commissioner of Patents
Please record the attached original d.

1. Name of conveying party(ies)
Ernst BAURHAN, Joachim ERGEMBACHER,
Uwe Josef VOGELBACHER, Matthias BRATE,
Hans THEOBALD, Matthias GESSER,
Additional name(s) of conveying party(ies)
attached /X/ Yes // No

3. Nature of conveyance:

/x/ Assignment // Merger
// Security Agreement // Change of Name

Execution date: 09/28/95

100280605

----- of receiving party(ies)

BASF Aktiengesellschaft
Street Address: 67056 Ludwigshafen
Germany

City: _____ State: _____ Zip: _____

Additional name(s) & address(es) attached?
// Yes /X/ No

4. Application number(s) or patent number(s):

If this document is being filed together with a new application,
the execution date of the application is:

10-19-1995

A. Patent Application No.(s)

B. Patent No.(s)

Additional numbers attached? // Yes /X/ No

5. Name and address of party to whom
correspondence concerning document should
be mailed:

Name: Herbert B. Kail
Internal Address:

Street Address: Kail & Weintraub
1101 Connecticut Ave. N.W.
City: Washington State: D.C. ZIP: 20036

6. Total number of applications and
and patents involved: // 1 //

7. Total Filing (37 CFR 3.41).... \$ 40.00

// Enclosed

8. // Authorized to be charged to
Deposit Account

DO NOT USE THIS SPACE

40E

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any
attached copy is a true copy of the original document.

020 MS 12/01/95 08537843

Herb B. Kail
Name of Person Signing

Herb B. Kail 1-88 40.00 CK October 19, 1995
Signature Date

Total number of pages // 1 //

FROM :

FAX NO. :

Jul. 18 2007 03:27PM P19

Karl-Otto WESTPHALEN
Helmut WALTER
Wilhelm HADEMACHER

PATENT
REEL: 8091 FRAME: 0667

U.S.A

ASSIGNMENT

O. Z. 0050143997

WHEREAS, we

Ernst Baumann, Falkenstrasse 6a, 67373 Dudenhofen
 Joachim Rheinheimer, Merziger Strasse 24, 67063 Ludwigshafen
 Uwe Josef Vogelbacher, Niedererndstrasse 56, 67071 Ludwigshafen
 Matthias Bratz, Schwabstrasse 2, 67345 Speyer
 Hans Theobald, Quelchstrasse 6, 67117 Limburgerhof
 Matthias Gerber, Brandenburger Strasse 24, 67117 Limburgerhof
 Karl-Otto Westphalen, Mausbergweg 58, 67346 Speyer
 Helmut Walter, Gruenstaedter Strasse 82, 67283 Obrigheim
 Wilhelm Rademacher, Austrasse 1, 67117 Limburgerhof
 Federal Republic of Germany
 citizens of the Federal Republic of Germany

have invented certain new and useful improvements in

3-(Hetero)arycarboxylic acid derivatives, their preparation and intermediates
 for their preparation

as fully set forth and described in the specification executed by us on

Serial No. . filed

preparatory to obtaining Letters Patent of the United States therefor; and

WHEREAS, BASF Aktiengesellschaft, having a place of business at 67056 Ludwigshafen, Federal Republic of Germany, is desirous of acquiring said invention and application and the exclusive right in and to the Letters Patent to be granted therefor.

NOW, THEREFORE, in consideration of the sum of One Dollar (\$1.00) to us in hand paid, the receipt whereof is hereby acknowledged, and other valuable consideration, we, the said

Ernst Baumann
 Joachim Rheinheimer
 Uwe Josef Vogelbacher
 Matthias Bratz
 Hans Theobald
 Matthias Gerber
 Karl-Otto Westphalen
 Helmut Walter
 Wilhelm Rademacher

have sold, assigned and transferred, and by these presents do sell, assign and transfer unto said BASF Aktiengesellschaft the full and exclusive right to the said invention and application and the entire right, title and interest in and to any and all Letters Patent which may be granted therefor, and in and to any and all divisions, reissues, continuations and extensions thereof.

We hereby authorize and request the Commissioner of Patents to issue the said Letters Patent, when granted, to said BASF Aktiengesellschaft, as the assignee of our entire right, title and interest in and to the same, for the sole use and behoof of said BASF Aktiengesellschaft, its successors and assigns.

FURTHER, we agree that we will communicate to said BASF Aktiengesellschaft, or its representatives, any facts known to us respecting said invention, and testify in any legal proceeding, sign all lawful papers, execute all divisional, continuation, substitution, renewal and related applications, make all rightful oaths and generally do everything possible to aid said BASF Aktiengesellschaft, its successors and assigns to obtain and enforce proper protection for said invention in the United States.

The undersigned hereby grant(s) the firm of Messrs. Kell & Weintraub, 1101 Connecticut Ave., N. W., Washington, D. C. 20036 the power to insert on this assignment any further identification, including the application number and filing date, which may be necessary or desirable in order to comply with the rules of the United States Patent and Trademark Office for recordation of this document.

IN TESTIMONY WHEREOF, we hereunto set our hands.

USA

Page 2

O. Z. 0050143997

09/28/1995

Date: Ernst BaumannDate: Uwe Josef WiegandDate: Hans TheobaldDate: Karl-Otto WestphalenDate: Wilhelm Rademacher

09/28/1995

Date: Joachim RheinheimerDate: Mathias BraizDate: Mathias GerberDate: Helmut Walter

01-08-2003

102328431

U.S. DEPARTMENT OF COMMERCE
U.S. Patent and Trademark Office

1-6-03

Form PTO-1595
(Rev. 10/02)
OMB No. 0851-0027 (exp. 6/30/2005)Tab settings

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):

MYOGEN, INC.

2. Name and address of receiving party(ies)

Name: GATX Ventures, Inc.

Internal Address: Suite 200

Additional name(s) of conveying party(ies) attached? Yes No

3. Nature of conveyance:

<input type="checkbox"/> Assignment	<input type="checkbox"/> Merger
<input checked="" type="checkbox"/> Security Agreement	<input type="checkbox"/> Change of Name
<input type="checkbox"/> Other _____	

Execution Date: 12/6/02

Street Address: 3687 Mt. Diablo Blvd.

City: Lafayette State: CA Zip: 94549

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is: _____

A. Patent Application No.(s) _____

See attached.

B. Patent No.(s) _____

See attached.

Additional numbers attached? Yes No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: GATX Ventures, Inc.

Attn: Legal Department
Internal Address: _____

6. Total number of applications and patents involved: 28

7. Total fee (37 CFR 3.41).....\$ 1120.00

 Enclosed Authorized to be charged to deposit account

8. Deposit account number: _____

Street Address: 16 Munson Road, 5th Floor

City: Farmington State: CT Zip: 06032

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9. Signature.

John C. Bombara, In-House Counsel
Name of Person Signing

12/30/02

Date

Total number of pages including cover sheet, attachments, and documents: 1

Mail documents to be recorded with required cover sheet information to:
Commissioner of Patents & Trademarks, Box Assessments
Washington, D.C. 20231

01/07/2003 070411 0000051 0943293

01 FC10421

1120.00 CP

PATENT
REEL: 013616 FRAME: 0001

FROM :

FAX NO. :

Jul. 18 2007 03:36PM P13

Form PTO-1595
Continuation of Item 2

Silicon Valley Bank
4410 Arapahoe, Suite 200
Boulder, CO 80303

PATENT
REEL: 013616 FRAME: 0002

SCHEDULE I-A TO GRANT OF SECURITY INTEREST**PATENTS**

PATENTS	Filing Date	App. No.	Country	Pat. No.	Issue Date
MYOG:005-US	4/1/1998	09/053,293	U.S.	6,218,597	4/17/2001
MYOG:006-US	9/26/1997	08/938,105	U.S.	6,363,151	3/5/2002
MYOG:007-US	5/26/1998	09/047,755	U.S.	6,203,776	3/20/2001
MYOG:013-US	6/19/1998	09/100,497	U.S.	5,998,458	12/7/1999
MYOG:020-US	10/15/1998	09/173,798	U.S.	6,201,185	3/13/2001
Abbott 43997	10/19/1995	537,843	U.S.	5,703,017	12/30/1997
Abbott 44751	9/30/1996	718,377	U.S.	5,840,722	11/24/1998
Abbott 45281	3/27/1997	809,899	U.S.	5,932,730	8/3/1999
Abbott 480/1171	3/30/2000	508,993	U.S.	6,329,384	12/11/2001
Abbott 480/1176	3/20/2000	508,989		6,352,992	3/5/2002
Abbott 480/1181	4/27/2000	530,131		6,197,780	3/6/2001

SCHEDULE 1-B TO GRANT OF SECURITY INTERESTPATENT APPLICATIONS

PATENTS	Filing Date	App. No.Country	Pat. No.	Issue Date
MYOG:004-USD1	4/25/2000	09/558,472	U.S.	
MYOG:004-USD2	10/1/2001	09/969,086	U.S.	
MYOG:020-USC1	1/29/2001	09/772,503	U.S.	
MYOG:020-USC2	3/13/2001	09/805,699	U.S.	
MYOG:023-US	10/16/1998	09/173,795	U.S.	
MYOG:024-US	11/10/1999	09/438,075	U.S.	
MYOG:024-USC1	1/9/2002	10/043,658	U.S.	
MYOG:026-US	10/15/1998	09/173,799	U.S.	
MYOG:026-US	8/20/2000	09/843,206	U.S.	
MYOG:028-US	7/18/2001	09/908,988	U.S.	
MYOG:029-US	4/16/1998	09/081,417	U.S.	
MYOG:034-US	9/27/2001	60/325,311	U.S.	
MYOG:036-US	2/13/2001	09/782,953	U.S.	
UTEC:005-US	8/11/2002	10/241,368	U.S.	
UTSD:662-US	8/13/1999	09/374,463	U.S.	
UTSD:729-US	11/7/2001	10/045,594	U.S.	
UTSD:803-US	5/30/2002	10/169,971	U.S.	

GRANT OF SECURITY INTEREST**PATENTS**

THIS GRANT OF SECURITY INTEREST, dated as of December 6, 2002, is executed by MYOGEN, INC., a Delaware corporation ("Debtor"), in favor of GATX VENTURES, INC. and SILICON VALLEY BANK (collectively, "Secured Party").

A. Pursuant to a Venture Loan and Security Agreement, dated on or about the date hereof (the "Agreement") among Debtor and the Secured Party, the Secured Party has agreed to extend certain credit facilities to Debtor upon the terms and subject to the conditions set forth therein;

B. Debtor owns the letters patent and/or applications for letters patent, of the United States, more particularly described on Schedules 1-A and 1-B annexed hereto as part hereof (collectively, the "Patents");

C. Pursuant to the Agreement, Debtor has granted to Secured Party a security interest in all right, title and interest of Debtor in and to the Patents, together with any reissue, continuation, continuation-in-part or extension thereof, and all proceeds thereof, including any and all causes of action which may exist by reason of infringement thereof for the full term of the Patents (the "Collateral"), to secure the prompt payment, performance and observance of the Obligations, as defined in the Agreement;

NOW, THEREFORE, for good and valuable consideration, receipt of which is hereby acknowledged, Debtor does hereby further grant to Secured Party a security interest in the Collateral to secure the prompt payment, performance and observance of the Obligations.

Debtor does hereby further acknowledge and affirm that the rights and remedies of Secured Party with respect to the security interest in the Collateral granted hereby are more fully set forth in the Agreement, the terms and provisions of which are hereby incorporated herein by reference as if fully set forth herein.

Secured Party's address is:

GATX Ventures, Inc.
3687 Mount Diablo Blvd., Suite 200
Lafayette, California 94549

With a copy to:

GATX Ventures, Inc.
16 Munson Road
Farmington, CT 06032

Silicon Valley Bank
4410 Arapahoe, Suite 200
Boulder, CO 80303

IN WITNESS WHEREOF, Debtor has caused this instrument to be executed as of the day and year first written above.

MYOGEN, INC.

By: Joseph L. Turner

Name: Joseph L. Turner
Title: Vice President, Finance and Administration
and Chief Financial Officer

01-25-2006

123b

FORM PTO-1595

(Rev. 08/05)
Office OMB No 0651-0077 (exp 06/30/2008)

REI



ET

U.S. DEPARTMENT OF COMMERCE
United States Patent and Trademark

103164670

To the Director of the U.S. Patent and Trademark Office: Please record the attached document(s) or the new address(es) below.

1. Name of conveying party(ies):
Silicon Valley Bank

2. Name and address of receiving party(ies): Myogen, Inc.

Additional name(s) of conveying party(ies) attached? Yes No

3. Nature of conveyance/Execution Date(s): 01/10/2006

Execution Date: 01/11/2006

Assignment Merger
 Security Agreement Change of Name
 Joint Research Agreement
 Government Interest Assignment
 Executive Order 9424, Confirmatory License
 Other Release

Name: Myogen, Inc.

Internal Address:

Street Address: 7575 W 103rd Ave., Suite 102

City: Westminster

State: Colorado

Country: USA

Zip: 80021

Additional name(s) & address(es) attached? Yes No

4. Application or patent number(s):

 This document is being filed together with a new application.

A. Patent Application No.(s):

09772603 10045664

B. Patent No.(s):

5703017	8024415	0167780	0032020
6363151	5840722	5932730	8740751
5998458	6203776	6218597	
6657104	6673768	6201165	
6329384	6372957	6352992	

Additional numbers attached? Yes No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Silicon Valley Bank

Internal Address: Loan Collateral HF154

Street Address: 3003 Tasman Drive

City: Santa Clara

State: CA Zip: 95054

Phone Number: (408) 654-4042

Fax Number: (408) 654-6313

Email Address: ldc@svbank.com

6. Total number of applications and patents involved: 23

7. Total fee (37 CFR 1.21 (h) & 3.41) \$920.00

Authorized to be charged by credit card
 Authorized to be charged to deposit account
 Enclosed
 None required (government interest not affecting title)

8. Payment Information

a. Credit Card Last 4 Numbers

Expiration Date

b. Deposit Account Number

Authorized User Name

9. Signature: John R. Russ

Signature

Date 7/11/07John R. Russ
Name of Person Signing

Total number of pages including cover sheet, attachments, and documents: 7

Documents to be recorded (including cover sheet) should be faxed to (703) 273-0140, or mailed to:
Mail Stop Assignment Recordation Services, Director of the USPTO, P.O. Box 1450, Alexandria, V.A. 22313-1450

01/25/2006 DDXRME 00000026 09772603

01 FC:0021 / 920.00 DD

PATENT

GRANT OF SECURITY INTERESTPATENTS

THIS GRANT OF SECURITY INTEREST, dated as of December 6, 2002, is executed by MYOGEN, INC., a Delaware corporation ("Debtor"), in favor of GATX VENTURES, INC. and SILICON VALLEY BANK (collectively, "Secured Party").

A. Pursuant to a Venture Loan and Security Agreement, dated on or about the date hereof (the "Agreement") among Debtor and the Secured Party, the Secured Party has agreed to extend certain credit facilities to Debtor upon the terms and subject to the conditions set forth therein;

B. Debtor owns the letters patent and/or applications for letters patent, of the United States, more particularly described on Schedules 1-A and 1-B annexed hereto as part hereof (collectively, the "Patents");

C. Pursuant to the Agreement, Debtor has granted to Secured Party a security interest in all right, title and interest of Debtor in and to the Patents, together with any reissue, continuation, continuation-in-part or extension thereof, and all proceeds thereof, including any and all causes of action which may exist by reason of infringement thereof for the full term of the Patents (the "Collateral"), to secure the prompt payment, performance and observance of the Obligations, as defined in the Agreement;

NOW, THEREFORE, for good and valuable consideration, receipt of which is hereby acknowledged, Debtor does hereby further grant to Secured Party a security interest in the Collateral to secure the prompt payment, performance and observance of the Obligations.

Debtor does hereby further acknowledge and affirm that the rights and remedies of Secured Party with respect to the security interest in the Collateral granted hereby are more fully set forth in the Agreement, the terms and provisions of which are hereby incorporated herein by reference as if fully set forth herein.

Secured Party' address is:

GATX Ventures, Inc.
3687 Mount Diablo Blvd., Suite 200
Lafayette, California 94549

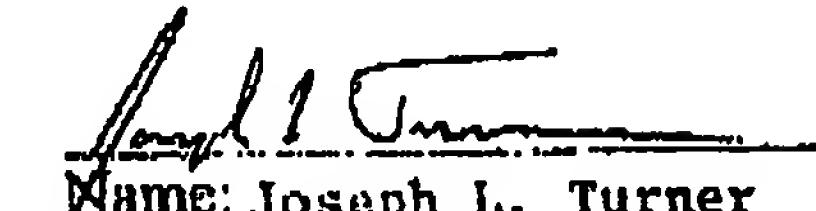
With a copy to:

GATX Ventures, Inc.
16 Munson Road
Farmington, CT 06032

Silicon Valley Bank
4410 Arapahoe, Suite 200
Boulder, CO 80303

IN WITNESS WHEREOF, Debtor has caused this instrument to be executed as of the day and year first written above.

MYOGEN, INC.

By: 

Name: Joseph L. Turner
Title: Vice President, Finance and Administration
and Chief Financial Officer

SCHEDULE I-A TO GRANT OF SECURITY INTERESTPATENTS

ATENTS	Filing Date	App. No.	Country	Pat. No.	Issue Date
YOG:005-US	4/1/1998	09/053,293	U.S.	6,218,597	4/17/2001
YOG:006-US	9/26/1997	08/938,105	U.S.	6,353,161	3/5/2002
YOG:007-US	5/26/1998	09/047,755	U.S.	6,203,776	3/20/2001
YOG:013-US	6/19/1998	09/100,497	U.S.	5,998,458	12/7/1999
YOG:020-US	10/15/1998	09/173,798	U.S.	6,201,165	3/13/2001
bbolt 43997	10/19/1995	537,843	U.S.	5,703,017	12/30/1997
bbolt 44751	9/30/1996	718,377	U.S.	5,840,722	11/24/1998
bbolt 45281	3/27/1997	809,699	U.S.	5,932,730	8/3/1999
bbolt 480/1171	3/30/2000	508,993	U.S.	6,329,384	12/11/2001
bbolt 480/1175	3/20/2000	508,989		6,352,992	3/5/2002
bbolt 480/1181	4/27/2000	530,131		6,197,780	3/6/2001

SCHEDULE I-B TO GRANT OF SECURITY INTERESTPATENT APPLICATIONS

PATENTS	Filing Date	App. No.Country	Pat. No.	Issue Date
MYOG:004-USD1	4/25/2000	09/558,472		U.S.
MYOG:004-USD2	10/1/2001	09/969,086		U.S.
MYOG:020-USC1	1/29/2001	09/772,503		U.S.
MYOG:020-USC2	3/13/2001	09/805,899		U.S.
MYOG:023-US	10/15/1998	09/173,795		U.S.
MYOG:024-US	11/10/1999	09/438,075		U.S.
MYOG:024-USC1	1/9/2002	10/043,658		U.S.
MYOG:025-US	10/15/1998	09/173,799		U.S.
MYOG:026-US	8/20/2000	09/643,206		U.S.
MYOG:028-US	7/18/2001	09/908,988		U.S.
MYOG:029-US	4/16/1998	09/061,417		U.S.
MYOG:034-US	9/27/2001	60/325,311		U.S.
MYOG:036-US	2/13/2001	09/782,953		U.S.
UTEC:005-US	9/11/2002	10/241,368		U.S.
UTSD:562-US	8/13/1999	09/374,453		U.S.
UTSD:729-US	11/7/2001	10/045,594		U.S.
UTSD:803-US	5/30/2002	10/159,971		U.S.

**RELEASE OF SECURITY AGREEMENT COVERING
INTERESTS IN PATENTS**

Silicon Valley Bank ("Secured Party"), hereby releases its security interest in the interests of Myogen, Inc. ("Assignor") in the patented works set forth in that certain **Grant Of Security Interest** dated December 6, 2002, executed by Assignor in favor of Secured Party recorded with the United States Department of Commerce, Patent and Trademark Office on January 6, 2003, Reel 013616, Frame(s) 0001.

Dated: **January 11, 2006**

SILICON VALLEY BANK

By: Maribel Higareda
Name: **Maribel Higareda**
Title: **Operations Supervisor**

Patent and Trademark

RECORDED: 01/23/2006

PATENT
REEL: 017480 FRAME: 0286

PATENT ASSIGNMENT

Electronic Version v1.1

Stylesheet Version v1.1

SUBMISSION TYPE:	NEW ASSIGNMENT					
NATURE OF CONVEYANCE:	RELEASE BY SECURED PARTY					
CONVEYING PARTY DATA						
<table border="1"> <tr> <td>Name</td> <td>Execution Date</td> </tr> <tr> <td>GATX Ventures, Inc. and Silicon Valley Bank</td> <td>01/13/2006</td> </tr> </table>		Name	Execution Date	GATX Ventures, Inc. and Silicon Valley Bank	01/13/2006	
Name	Execution Date					
GATX Ventures, Inc. and Silicon Valley Bank	01/13/2006					
RECEIVING PARTY DATA						
Name:	Myogen, Inc.					
Street Address:	7575 West 103rd Avenue, #102					
City:	Westminster					
State/Country:	COLORADO					
Postal Code:	80021					
PROPERTY NUMBERS Total: 28						
Property Type	Number					
Patent Number:	6218597					
Patent Number:	6353151					
Patent Number:	6203776					
Patent Number:	699B458					
Patent Number:	6201165					
Patent Number:	5703017					
Patent Number:	5840722					
Patent Number:	69327,10					
Patent Number:	632938-1					
Patent Number:	6352992					
Patent Number:	8497780					
Application Number	00558472					
Application Number	00558472					
Application Number	00558472					
Application Number	00558472					

OP-S4120.00 S218597

PATENT
REEL: 017025 FRAME: 0877

500071832

Application Number:	09173795
Application Number:	09438075
Application Number:	10043658
Application Number:	09173790
Application Number:	09543206
Application Number:	09500988
Application Number:	09061417
Application Number:	60325311
Application Number:	09782953
Application Number:	10241368
Application Number:	09374453
Application Number:	10045594
Application Number:	10159971

CORRESPONDENCE DATA

Fax Number: (303)672-0101

Correspondence will be sent via US Mail when the fax attempt is unsuccessful.

Phone: 3036720106

Email: bschoenfeld@kkofirm.com

Correspondent Name: Brad Schoenfeld
Address Line 1: 1675 Broadway, Suite 750
Address Line 4: Denver, CO 80202

NAME OF SUBMITTER: Brad Schoenfeld

Total Attachments: 3

source=Myogen - Release of Security Interest (Patents) #page1.tif

source=Myogen - Release of Security Interest (Patents) #page2.tif

source=Myogen - Release of Security Interest (Patents) #page3.tif

TERMINATION
OF
SECURITY INTEREST IN PATENTS

This Termination of Security Interest in Patents (the "Termination") is executed by GATX VENTURES, INC. as Agent for GATX VENTURES, INC. and SILICON VALLEY BANK (the "Secured Parties"), in favor of MYOGEN, INC., a Delaware corporation (the "Debtor"), and is effective as of January 13, 2006.

RECITALS

A. Debtor and the Secured Party entered into a certain Venture Loan and Security Agreement, dated as of December 26, 2002 (the "Agreement").

B. The Grant of Security Interest in Patents, relating to the Agreement, was filed with the Patent and Trademark Office on January 6, 2003, at Reel 013616, Frame 0001.

C. Debtor has repaid all amounts due under the Agreement.

The Secured Parties therefore expressly terminate their security interest in the Collateral, including without limitation, the patents and patent applications listed on Schedule 1-A and 1-B attached hereto.

IN WITNESS WHEREOF, this Termination is executed as of the date first above written.

GATX VENTURES, INC., as Agent

By: Maney Keating
Name: Maney Keating
Title: Vice President

SCHEDULE I-A TO GRANT OF SECURITY INTERESTPATENTS

PATENTS	Filing Date	App. No.	Country	Pat. No.	Issue Date
MYOG:005-US	4/1/1998	09/053,293	U.S.	6,218,597	4/17/2001
MYOG:006-US	8/26/1997	08/938,105	U.S.	6,353,151	3/5/2002
MYOG:007-US	5/28/1998	09/047,766	U.S.	6,203,776	3/20/2001
MYOG:013-US	6/19/1998	08/100,487	U.S.	5,988,458	12/7/1999
MYOG:020-US	10/15/1998	09/173,708	U.S.	6,201,185	3/13/2001
Abbott 43987	10/19/1995	537,843	U.S.	5,703,017	12/30/1997
Abbott 44761	9/30/1996	718,377	U.S.	5,840,722	11/24/1998
Abbott 45281	3/27/1997	809,699	U.S.	5,932,730	8/3/1999
Abbott 480/1171	3/30/2000	508,953	U.S.	6,329,384	12/11/2001
Abbott 480/1178	3/20/2000	508,989		6,352,092	3/5/2002
Abbott 480/1181	4/27/2000	530,131		6,197,760	3/8/2001

U.S. GOVERNMENT SECURITY GRANT (1449000) 0001 (1449000)

PATENT
REEL: 017026 FRAME: 0880

SCHEDULE 1-B TO GRANT OF SECURITY INTERESTPATENT APPLICATIONS

PATENTS	Filing Date	App. No. Country	Pat. No.	Issue Date
MYOG:004-USD1	4/25/2000	09/558,472	U.S.	
MYOG:004-USD2	10/1/2001	08/989,086	U.S.	
MYOG:020-USC1	1/29/2001	09/772,503	U.S.	
MYOG:020-USC2	9/13/2001	09/805,699	U.S.	
MYOG:023-US	10/15/1998	09/173,795	U.S.	
MYOG:024-US	11/10/1999	08/438,075	U.S.	
MYOG:024-USC1	1/8/2002	10/043,658	U.S.	
MYOG:025-US	10/15/1998	09/173,799	U.S.	
MYOG:026-US	8/20/2000	09/643,208	U.S.	
MYOG:028-US	7/18/2001	09/908,908	U.S.	
MYOG:029-US	4/16/1998	09/061,417	U.S.	
MYOG:034-US	9/27/2001	09/325,311	U.S.	
MYOG:036-US3	2/13/2001	09/782,953	U.S.	
UTEC:006-US	9/11/2002	10/241,358	U.S.	
UTSD:562-US	8/13/1999	09/374,453	U.S.	
UTSD:729-US	11/7/2001	10/045,594	U.S.	
UTSD:803-US	6/30/2002	10/159,971	U.S.	

RECORDATION FORM COVER SHEET

PATENTS ONLY

To the Director of the U.S. Patent and Trademark Office, Please record the attached documents or the new address(es) below.

1. Name of conveying party(ies)

BASF Aktiengesellschaft

Additional name(s) of conveying party(ies) attached? Yes No

2. Nature of conveyance/Execution Date(s):

Execution Date(s) October 17, 2006

Assignment Merger

Security Agreement Change of Name

Joint Research Agreement

Government Interest Assignment

Executive Order 9424, Confirmatory License

Other

4. Application or patent number(s):

A. Patent Application No.(s)

 This document is being filed together with a new application.

B. Patent No.(s)

5,703,017

Additional numbers attached? Yes No

5. Name and address to whom correspondence concerning document should be mailed:

Name: Gayle B. O'Brien

Internal Address: Abbott Bioresearch Center

Street Address: 100 Research Drive

City: Worcester

State: MA

Zip: 01805-4314

Phone Number: (508) 688-8053

Fax Number: (508) 688-8110

Email Address: gayle.o'brien@abbott.com

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 1.21(h) & 3.41) \$ 40.00

Authorized to be charged by credit card

Authorized to be charged to deposit account

Enclosed

None required (government interest not affecting title)

B. Payment Information

a. Credit Card Last 4 Numbers _____
Expiration Date _____

b. Deposit Account Number 01-0025

Authorized User Name Gayle B. O'Brien

9. Signature: Gayle B. O'Brien

Signature

Oct 17, 2006

Date

Gayle B. O'Brien

Name of Person Signing

Total number of pages including cover sheet, attachments, and documents.

5

Documents to be recorded (including cover sheet) should be faxed to (571) 273-0140, or mailed to:
Mail Stop Assignment Registration Services, Director of the USPTO, P.O. Box 1450, Alexandria, VA 22313-1450

700294393

PATENT
REEL: 018454 FRAME: 0430

ASSIGNMENT

WHEREAS, BASF Aktiengesellschaft hereinafter called the "Assignors", has acquired through Assignment from the inventors the inventions described in the United States Patent 5,703,017 entitled "3 (Hct) arylcarboxylic acid derivatives, their preparation and intermediates for their preparation", which issued on December 30th, 1997;

WHEREAS, Abbott GmbH & Co. KG, a corporation organized and existing under the laws of Germany, having a place of business at Max-Planck-Ring 2, 65205 Wiesbaden, Germany, hereinafter called the "Assignee", desires to acquire the entire right, title and interest in and to the invention and to the patent and all patents, foreign and domestic, which may be obtained for said invention, as set forth below;

NOW, THEREFORE, in consideration of valuable and legally sufficient consideration, the receipt of which by the Assignors from the Assignee is hereby acknowledged, the Assignors have sold, assigned and transferred, and by these presents do sell, assign and transfer to the Assignee, the entire right, title and interest for the United States and elsewhere in and to the inventions and the patent, and any patents that may issue for said invention in the United States and elsewhere; together with the entire right, title and interest in and to said invention and all patent applications, patents, utility models and designs therefor in all countries foreign to the United States, including the full right to claim for any such application all benefits and priority rights under any

applicable convention; together with the entire right, title and interest in and to all continuations, divisions, renewals and extensions of any of the patent applications, patents, utility models and designs defined above; to have and to hold for sole and exclusive use and benefit of the Assignee, its successors and assigns, to the full end of the term or terms for all such patents.

The Assignors hereby covenant and agree, for both the Assignors and the Assignors legal representative, that Assignors have the full right to convey the interest assigned by this Assignment and that the Assignors will execute and deliver to the Assignee any and all additional papers which may be requested by the Assignee to carry out the terms of this Agreement.

The Commissioner of Patents and Trademarks is hereby authorized and requested to issue patents to the Assignee in accordance with the terms of this Assignment.

IN TESTIMONY WHEREOF, the Assignors have executed this agreement.

ASSIGNOR: BASF Aktiengesellschaft

Signature: Mr. R. Röder 

Print name: BBB. Köster - BBB. Cimnick

For: BASF Aktiengesellschaft
67056 Ludwigshafen

Germany

007.10.17.1114

W. S. F. 11

ACKNOWLEDGEMENT:

On this 17th day of October, 2006, Dr. Reinhold Köster and Dr. Thomas Cimniak personally appeared before me, executing the foregoing Assignment, and fully acknowledged to me that such Assignment was executed by his/her free act and deed for the uses and purposes therein expressed.

Karin Werner
Witness signature

Karin Werner
Witness name (please print)

EXHIBIT

B



Advancing Therapeutics.
Improving Lives.

Linnea Tanner
Director, Regulatory Affairs

13 December 2006

Norman L. Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Food and Drug Administration
Center for Drug Evaluation & Research
Central Document Room
5901-B Ammendale Rd.
Beltsville, MD 20705-1266

Subject: NDA 22-081 (022081-0000)
LETAIRIS™ (ambrisentan) Tablets

NEW DRUG APPLICATION
Original Submission

Dear Dr. Stockbridge:

Pursuant to the Paragraph 505(b)(1) of the Federal, Food, Drug and Cosmetic Act (the ACT) and 21 CFR 314.50, Gilead Sciences, Inc. (Gilead) hereby submits a New Drug Application (NDA) for LETAIRIS (ambrisentan) Tablets, 5 and 10 mg. Ambrisentan is a non-sulfonamide, propanoic acid-class, endothelin receptor antagonist (ERA) that is selective for the endothelin type A (ET_A) receptor. LETAIRIS is indicated for the treatment of pulmonary arterial hypertension (WHO Group 1) to improve exercise capacity, delay clinical worsening and improve symptoms.

Myogen, Inc. was acquired by Gilead Sciences, Inc. and became a wholly owned subsidiary known as Gilead Colorado, Inc., effective November 17, 2006. Thus, the NDA applicant is Gilead Sciences, Inc., which assumes all the responsibilities and obligations of the NDA. However, the name Myogen, Inc. is used throughout the NDA for historical reasons and because of the timing of acquisition.

Request for Priority Review

Ambrisentan was granted Fast Track designation for the treatment of pulmonary arterial hypertension (PAH) on February 15, 2006; therefore, we request that this application be given priority review. PAH is a rare, serious and life-threatening disease for which there is no cure. Although there are other therapies currently approved for this disease, there still is an unmet medical need for the treatment of PAH. LETAIRIS is an alternative, therapeutic option for these patients that has the potential to provide significant benefit over currently authorized therapies for the following reasons:

Confidentiality Statement

The confidential information contained in this document is the property of Gilead Sciences, Inc. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from Gilead Sciences, Inc.

- Improved effects on exercise capacity, an efficacy measure that has been shown to correlate with and be prognostic of long-term survival
- Significant delay of the clinical worsening of PAH, an efficacy measure of disease progression in this ultimately fatal disease
- Improved effects on symptoms associated with PAH (WHO functional class, Borg dyspnea index, and SF-36® physical function scale)
- Low incidence of liver function test (LFT) abnormalities, a serious toxicity that can lead to discontinuation of treatment with other ERA therapies
- Potential to provide benefit to PAH patients who have previously discontinued ERA therapy due to LFT abnormalities
- No clinically significant cytochrome P450 (CYP) enzyme-related interactions with several drugs that are currently contraindicated, less effective, or associated with significant safety issues when co-administered with other PAH therapies

Orphan Drug Designation

Ambrisentan was granted orphan drug designation (Designation Request #04-1836) for the treatment of PAH and, therefore, qualifies for seven (7) years of exclusive marketing rights pursuant to Section 527 of the ACT (21 U.S.C. 360 cc). A letter dated December 07, 2006 was submitted to the Office of Orphan Drug Products Development to transfer the orphan designation from Myogen, Inc. to Gilead Sciences, Inc.

Application Fee

Under Section 736(a)(1)(E) of the ACT, this NDA is not subject to an application fee because LETAIRIS (ambrisentan) Tablets, 5 and 10 mg, is indicated for the treatment of a rare disease or condition designated under Section 526 of the ACT (orphan drug designation).

Pediatric Data

Since ambrisentan was granted orphan designation for PAH under Section 526 of the ACT (21 U.S.C. 360bb), no pediatric data is submitted in the original NDA 22-081. Pediatric data is not required for applications to market the product for the orphan-designated indications and a waiver is not needed [21 CFR 314.55(d) for NDAs and 601.27(d) for BLAs]. As agreed during the Pre-NDA meeting on May 19, 2006, Gilead will submit a pediatric study request and a proposal for a pediatric study following the NDA submission so that the Division can issue a written request to initiate pediatric studies that will be used to support pediatric exclusivity.

Proposed Proprietary Name

The proposed proprietary name of LETAIRIS was submitted for review on November 4, 2005 in Serial No. 094 of IND 64,915.

Application Format

The archive copy of NDA 22-081 (eCTD 022081-0000) is provided in its entirety as an electronic submission using the electronic Common Technical Document (eCTD) format in accordance with the guidance *M2: eCTD: Electronic Common Technical Document Specification* and as agreed in the Pre-NDA meeting on May 19, 2006. Gilead has notified the FDA Denver District office about the NDA submission in the eCTD format. A copy of the field copy certification is provided in Section m1.3.2.

Please refer to an attachment (Summary of FDA Interactions and Commitments for Ambrisentan Development Plan) to this cover letter for any other agreements of the format and content of the NDA, including the electronic datasets.

Required Regulatory Forms applicable to this submission have been included in the electronic submission and are signed electronically. Pursuant to 21 CFR 11.100, Gilead certifies that all electronic signatures executed by our employees, agents, or representatives, located anywhere in the world, are the legally binding equivalent of traditional handwritten signatures.

This submission is provided on a DVD-ROM and is approximately 4.2 GB. Gilead certifies that the submission is virus free as defined by the 11 December 2006 version of the McAfee® VirusScan® Enterprise-program, Version 8.0.0, Scan Engine 5100, with 4916 virus definitions.

Annotated ECG Waveform Data

In accordance with the instructions available on the CDER Electronic Regulatory Submissions and Review website, and confirmation with the Office of Business Process Support (OBPS), Gilead has submitted annotated ECG waveform data in XML format to the E-Scribe ECG Warehouse. These files are representative of data collected in a Phase 1 QTc study (AMB-104), and the two pivotal Phase 3 studies (AMB-320 and AMB-321). These data files are now available for your review through E-Scribe ECG Warehouse.

Contact Information

Regulatory Contact:

Linnea Tanner
Director, Regulatory Affairs
Gilead Colorado, Inc.
7575 West 103rd Ave., #102
Westmister, CO 80021-5426
Phone (direct): 303-410-3243
Facsimile: 303-410-3354
e-mail: linnea.tanner@gilead.com

Regulatory Contact - CMC:

Todd Marshall
Associate Director, CMC Regulatory
Gilead Colorado, Inc.
7575 West 103rd Ave., #102
Westmister, CO 80021-5426
Phone (direct): 303-464-3958
Facsimile: 303-410-3354
e-mail: todd_marshall@gilead.com

Technical Contact for the eCTD:

Liam Curran
Senior Manager, Regulatory Operations
Gilead Colorado, Inc.
7575 West 103rd Ave., #102
Westmister, CO 80021-5426
Phone (direct): 303-410-3206
Facsimile: 303-410-3354
e-mail: liam.curran@gilead.com

Please do not hesitate to contact me with any questions.

Sincerely,

{See appended electronic signature page}

Linnea Tanner
Director, Regulatory Affairs
Phone: 303-410-3243
Fax: 303-410-3354

Attachment: Summary of FDA Interactions and Commitments for Ambrisentan Development Plan



GILEAD

Document Approval Certificate

THE PRECEDING DOCUMENT HAS BEEN ELECTRONICALLY SIGNED BY:

UserName: ltanner

Title: Director, Regulatory Affairs

Date: Wednesday, 13 December 2006, 05:30 PM Mountain Daylight Time

Meaning: Document approved and signed

EXHIBIT

C



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-081

Gilead Sciences, Inc.
Attention: Ms. Linnea Tanner
Director, Regulatory Affairs
Gilead Colorado
7575 West 103rd Ave., Suite #102
Westminster, CO 80021-5426

Dear Ms. Tanner:

Please refer to your new drug application (NDA) dated December 13, 2006 submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Letairis (ambrisentan) 5 and 10 mg Tablets.

We acknowledge receipt of your submission(s) dated January 11 and 26, February 28, March 2, 13, 16, and 26, April 6, 17, and 24, May 1, 11, 14, 15, and 30, and June 1, 6, and 11, 2007.

This new drug application provides for the use of Letairis (ambrisentan) 5 and 10 mg Tablets for the treatment of pulmonary arterial hypertension (WHO Group 1) in patients with WHO class II or III symptoms to improve exercise capacity and delay clinical worsening.

We have completed our review of this application. It is approved with restrictions to assure safe use under the provisions of the Subpart H regulations (21 CFR 314.520), effective on the date of this letter, for use as recommended in the enclosed labeling text, Medication Guide, RiskMAP, and carton and container labels. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced restricted distribution approval regulations.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/oc/datacouncil/spl.html>, that is identical in content to the enclosed labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, Medication Guide, RiskMAP, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "FPL for approved NDA 22-081." Approval of this submission by FDA is not required before the labeling is used.

The Pediatric Research Equity Act is not applicable to drugs granted orphan drug designation.

The postmarketing study commitments that have been agreed upon based on your written correspondence dated 6/15/07 are listed below:

1. Gilead agrees to conduct a study examining the effects of LETAIRIS on 6-minute walk distance at peak and trough plasma concentrations, and further agrees to reach agreement on an appropriate study design with the Division.

Protocol Submission:	by 10/1/2007
Study Start:	by 06/2008
Final Report Submission:	by 12/2009
2. Gilead agrees to submit the results of the Phase 1 ketoconazole drug interaction study that has already been completed.

Final Report Submission:	by 10/2007
--------------------------	------------
3. Gilead agrees to a post-approval commitment to explore the interaction potential of strong inhibitors of CYP2C19 (e.g. omeprazole) on ambrisentan pharmacokinetics in humans. Gilead further agrees to explore the interaction potential of cyclosporine A (strong inhibitor of OATP and P-gp) and rifampin (inhibitor of OATP and inducer of P-gp, CYPs 3A and 2C19) on ambrisentan pharmacokinetics in humans.

Protocol Submission:	by 10/1/2007
Study Start:	by 04/2008
Final Report Submission:	by 12/2008

This commitment might also be addressed by analysis of existing data.
4. With regard to the RiskMAP, Gilead agrees to submit to the FDA by July 15, 2007, the following documents:
 - i. The pregnancy exposure root cause analysis plan including the questionnaire that will be used in the analysis plan;
 - ii. The patient and prescriber knowledge, attitude, and behavior survey tools for the RiskMAP evaluation plan;
 - iii. The Pharmacy Standard Operating Procedures (SOPs); and
 - iv. The Pharmacy Audit Plan.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **“Postmarketing Study Commitment Protocol”**, **“Postmarketing Study Commitment Final Report”**, or **“Postmarketing Study Commitment Correspondence.”**

As required by 21 CFR 314.550, submit all promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement. Send two copies of all promotional materials directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

We have determined that Letairis poses a serious and significant public health concern relating to women of child-bearing potential and patients with liver impairment. This concern requires development and distribution of a Medication Guide under 21 CFR 208 in order to prevent serious adverse effects, inform patients of

information concerning risks that could affect their decision to use or continue to use the drug, and/or assure effective use of the drug.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for every patient who is dispensed Letairis. Therefore, format the proposed Medication Guide in a manner that will assure its appropriate distribution to patients and include a plan to ensure distribution. In addition, submit proposed container and/or carton labels for Letairis that include a prominent and conspicuous instruction to provide the Medication Guide to each patient dispensed the drug. The labels must state how the Medication Guide is provided (e.g., affixed on the container, provided with the product, etc.).

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, please call Dan Brum, PharmD, MBA, Regulatory Project Manager, at (301)796-0578.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Robert Temple
6/15/2007 04:56:32 PM

EXHIBIT

D



Advancing Therapeutics.
Improving Lives.

LETTER OF RELIANCE

Mail Stop Hatch-Waxman PTE
Office of Patent Legal Administration
Room MDW 7D55
600 Dulany Street (Madison Building)
Alexandria, VA 22314

Attn: Mary C. Till, Examiner
Office of Patent Legal Administration

Gilead Sciences, Inc., Licensee of the exclusive rights to U.S. Patent No. 5,703,017 ("U.S. '017"), authorizes **Abbott Laboratories**, Licenser and record-owner of U.S. '017, to rely on the activities of Gilead Sciences, Inc. supporting FDA approval of LETAIRIS™ (ambrisentan) product (5 and 10 mg tablets), for the purpose of obtaining extension of patent term of U.S. '017, as provided under 35 U.S.C. §156(d)(1), 37 C.F.R. §1.730 and MPEP 2752.

Date: 8/2/07

Authorized by Gilead Sciences, Inc.

By:


Richard J. Gorczynski, PhD
SVP, Cardiovascular Therapeutics

EXHIBIT

E

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LETAIRIS™ tablets safely and effectively. See full prescribing information for LETAIRIS.

LETAIRIS (ambrisentan) tablets for oral use

Initial U.S. Approval: 2007

WARNING: POTENTIAL LIVER INJURY AND CONTRAINDICATION IN PREGNANCY

See full prescribing information for complete boxed warning.

- Elevations of liver aminotransferases (ALT, AST) have been reported with LETAIRIS and serious liver injury has been reported with related drugs.
- Monitor liver aminotransferases monthly and discontinue LETAIRIS if >5 x ULN or if elevations are accompanied by bilirubin >2 x ULN or by signs or symptoms of liver dysfunction.
- May cause fetal harm if taken during pregnancy (4.1)
- Must exclude pregnancy before the start of treatment (2.2)
- Prevent pregnancy thereafter by the use of two reliable methods of contraception (2.2)

INDICATIONS AND USAGE

LETAIRIS is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (WHO Group 1) in patients with WHO class II or III symptoms to improve exercise capacity and delay clinical worsening (1).

DOSAGE AND ADMINISTRATION

- Initiate treatment at 5 mg once daily with or without food, and consider increasing the dose to 10 mg once daily if 5 mg is tolerated (2.1).
- Treat women of child-bearing potential only after a negative pregnancy test and treat only women who are using two reliable methods of contraception unless the patient has had a tubal sterilization or a Copper T 380A IUD or LNG 20 IUD inserted. Obtain monthly pregnancy tests (2.2).
- Not recommended in patients with moderate or severe hepatic impairment (2.3)

DOSAGE FORMS AND STRENGTHS

- 5 mg and 10mg film-coated, unscored tablets (3)

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING – POTENTIAL LIVER INJURY; CONTRAINDICATED IN PREGNANCY

- INDICATIONS AND USAGE
- DOSAGE AND ADMINISTRATION
 - Adult Dosage
 - Women of Childbearing Potential
 - Pre-existing Hepatic Impairment
- DOSAGE FORMS AND STRENGTHS
- CONTRAINDICATIONS
 - Pregnancy Category X
- WARNINGS AND PRECAUTIONS
 - Potential Liver Injury
 - Hematological Changes
 - Peripheral Edema
 - Co-administration of LETAIRIS and Cyclosporine A
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 - Cyclosporine A
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 - Warfarin
 - Sildenafil
- USE IN SPECIFIC POPULATIONS
 - Pregnancy
 - Nursing Mothers
 - Pediatric Use
 - Geriatric Use
 - Renal Impairment
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CONTRAINDICATIONS

- Do not administer LETAIRIS to a pregnant woman because it can cause fetal harm (4.1).

WARNINGS AND PRECAUTIONS

- Decreases in hemoglobin have been observed within the first few weeks; measure hemoglobin at initiation, at 1 month, and periodically thereafter (5.2).
- Mild to moderate peripheral edema (5.3)
- Use caution when LETAIRIS is co-administered with cyclosporine A (5.4 and 7).
- Use caution when LETAIRIS is co-administered with strong CYP3A and 2C19 inhibitors (5.5 and 7).

ADVERSE REACTIONS

Most common placebo-adjusted adverse reactions are peripheral edema, nasal congestion, sinusitis, flushing, palpitations, abdominal pain, and constipation (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at (1-800-GILEAD5, Option 3) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- No significant interactions of LETAIRIS with warfarin or sildenafil have been observed (7).
- Other potential interactions are not well characterized, but, based on *in vitro* data, interactions with P-glycoprotein (P-gp), the Organic Anion Transport Protein (OATP), CYP3A4, and CYP2C19 inhibitors, and uridine 5'-diphosphate glucuronosyltransferases (UGTs) would be expected (7).

USE IN SPECIFIC POPULATIONS

- Pregnancy Category X: LETAIRIS is contraindicated in pregnant women (4.1 and 8.1).
- Nursing mothers: Breastfeeding while receiving LETAIRIS is not recommended (8.3).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling (Medication Guide)

Revised: [06/2007]

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

14.1 Pulmonary Arterial Hypertension (PAH)

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14.3 Use in Patients with Prior Endothelin Receptor Antagonist Related Liver Function Abnormalities

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

17.1 Importance of Preventing Pregnancy

17.2 Adverse Liver Effects

17.3 Hematological Change

17.4 Administration

17.5 FDA-Approved Medication Guide

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: POTENTIAL LIVER INJURY

LETAIRIS (ambrisentan) can cause elevation of liver aminotransferases (ALT and AST) to at least 3 times the upper limit of normal (ULN). LETAIRIS treatment was associated with aminotransferase elevations $>3 \times$ ULN in 0.8% of patients in 12-week trials and 2.8% of patients including long-term open-label trials out to one year. One case of aminotransferase elevations $>3 \times$ ULN has been accompanied by bilirubin elevations $>2 \times$ ULN. Because these changes are a marker for potentially serious liver injury, serum aminotransferase levels (and bilirubin if aminotransferase levels are elevated) must be measured prior to initiation of treatment and then monthly.

In the post-marketing period with another endothelin receptor antagonist (ERA), bosentan, rare cases of unexplained hepatic cirrhosis were reported after prolonged (>12 months) therapy. In at least one case with bosentan, a late presentation (after >20 months of treatment) included pronounced elevations in aminotransferases and bilirubin levels accompanied by non-specific symptoms, all of which resolved slowly over time after discontinuation of the suspect drug. This case reinforces the importance of strict adherence to the monthly monitoring schedule for the duration of treatment.

Elevations in aminotransferases require close attention. LETAIRIS should generally be avoided in patients with elevated aminotransferases ($>3 \times$ ULN) at baseline because monitoring liver injury may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin $>2 \times$ ULN, treatment should be stopped. There is no experience with the re-introduction of LETAIRIS in these circumstances.

CONTRAINDICATION: PREGNANCY

LETAIRIS is very likely to produce serious birth defects if used by pregnant women, as this effect has been seen consistently when it is administered to animals [see *Contraindications (4.1)*]. Pregnancy must therefore be excluded before the initiation of treatment with LETAIRIS and prevented thereafter by the use of at least two reliable methods of contraception unless the patient has had a tubal sterilization or Copper T 380A IUD or LNG 20 IUD inserted, in which case no other contraception is needed. Obtain monthly pregnancy tests.

Because of the risks of liver injury and birth defects, LETAIRIS is available only through a special restricted distribution program called the LETAIRIS Education and Access Program (LEAP), by calling 1-866-664-LEAP (5327). Only prescribers and pharmacies registered with LEAP may prescribe and distribute LETAIRIS. In addition, LETAIRIS may be dispensed only to patients who are enrolled in and meet all conditions of LEAP [see *WARNINGS, Prescribing and Distribution Program for LETAIRIS*].

1 INDICATIONS AND USAGE

LETAIRIS is indicated for the treatment of pulmonary arterial hypertension (WHO Group 1) in patients with WHO class II or III symptoms to improve exercise capacity and delay clinical worsening.

2 DOSAGE AND ADMINISTRATION

2.1 Adult Dosage

Initiate treatment at 5 mg once daily with or without food, and consider increasing the dose to 10 mg once daily if 5 mg is tolerated.

Tablets may be administered with or without food. Tablets should not be split, crushed, or chewed. Doses higher than 10 mg once daily have not been studied in patients with pulmonary arterial hypertension (PAH). Liver function tests should be measured prior to initiation and during treatment with LETAIRIS [see *Warnings and Precautions (5.1)*].

2.2 Women of Childbearing Potential

Treat women of childbearing potential only after a negative pregnancy test and treat only women who are using two reliable methods of contraception unless the patient has had a tubal sterilization or a Copper T 380A IUD or LNG 20 IUD inserted. In those cases, no other contraception is needed. Pregnancy tests should be obtained monthly in women of childbearing potential taking LETAIRIS [see *Contraindications (4.1)*].

2.3 Pre-existing Hepatic Impairment

LETAIRIS is not recommended in patients with moderate or severe hepatic impairment [see *Special Populations (8.7)*]. Use caution in patients with mild hepatic impairment.

3 DOSAGE FORMS AND STRENGTHS

LETAIRIS is available as 5 mg and 10 mg film-coated, unscored tablets.

4 CONTRAINDICATIONS

4.1 Pregnancy Category X

LETAIRIS may cause fetal harm when administered to a pregnant woman. Ambrisentan was teratogenic at oral doses of ≥ 15 mg/kg/day in rats and ≥ 7 mg/kg/day in rabbits; it was not studied at lower doses. In both species, there were abnormalities of the lower jaw and hard and soft palate, malformation of the heart and great vessels, and failure of formation of the thymus and thyroid. Teratogenicity is a class effect of endothelin receptor antagonists. There are no data on the use of LETAIRIS in pregnant women.

LETAIRIS is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Pregnancy must be excluded before the initiation of treatment with LETAIRIS and prevented thereafter by the use of two reliable methods of contraception [see *Dosage and Administration (2.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Potential Liver Injury (see BOXED WARNING)

Treatment with endothelin receptor antagonists has been associated with dose-dependent liver injury manifested primarily by elevation of serum aminotransferases (ALT or AST), but sometimes accompanied by abnormal liver function (elevated bilirubin). The combination of aminotransferases greater than 3-times the upper limit of normal ($>3 \times \text{ULN}$) and total bilirubin $>2 \times \text{ULN}$ is a marker for potentially serious hepatic injury.

Liver function tests were closely monitored in all clinical studies with LETAIRIS. For all LETAIRIS-treated patients (N=483), the 12-week incidence of aminotransferases $>3 \times \text{ULN}$ was 0.8% and $>8 \times \text{ULN}$ was 0.2%. For placebo-treated patients, the 12-week incidence of aminotransferases $>3 \times \text{ULN}$ was 2.3% and $>8 \times \text{ULN}$ was 0.0%. The 1-year rate of aminotransferase elevations $>3 \times \text{ULN}$ with LETAIRIS was 2.8% and $>8 \times \text{ULN}$ was 0.5%. One case of aminotransferase elevations $>3 \times \text{ULN}$ has been accompanied by bilirubin elevations $>2 \times \text{ULN}$.

Liver chemistries must be measured prior to initiation of LETAIRIS and at least every month thereafter. If there are aminotransferase elevations $>3 \times \text{ULN}$ and $\leq 5 \times \text{ULN}$, they should be re-measured. If the confirmed level is $>3 \times \text{ULN}$ and $\leq 5 \times \text{ULN}$, reduce the daily dose or interrupt treatment and continue to monitor every two weeks until the levels are $<3 \times \text{ULN}$. If there are aminotransferase elevations $>5 \times \text{ULN}$ and $\leq 8 \times \text{ULN}$, LETAIRIS should be discontinued and monitoring should continue until the levels are $<3 \times \text{ULN}$. LETAIRIS can then be re-initiated with more frequent measurement of aminotransferase levels. If there are aminotransferase elevations $>8 \times \text{ULN}$, treatment should be stopped and re-initiation should not be considered.

LETAIRIS is not recommended in patients with elevated aminotransferases ($>3 \times \text{ULN}$) at baseline because monitoring liver injury may be more difficult. If aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant abdominal discomfort, itching, or jaundice) or increases in bilirubin $>2 \times \text{ULN}$, LETAIRIS treatment should be stopped. There is no experience with the re-introduction of LETAIRIS in these circumstances.

5.2 Hematological Changes

Decreases in hemoglobin concentration and hematocrit have followed administration of other endothelin receptor antagonists and were observed in clinical studies with LETAIRIS. These decreases were observed within the first few weeks of treatment with LETAIRIS, and stabilized thereafter. The mean decrease in hemoglobin from baseline to end of treatment for those patients receiving LETAIRIS in the 12-week placebo-controlled studies was 0.8 g/dL.

Marked decreases in hemoglobin ($>15\%$ decrease from baseline resulting in a value below the lower limit of normal) were observed in 7% of all patients receiving LETAIRIS (and 10% of patients receiving 10 mg) compared to 4% of patients receiving placebo.

The cause of the decrease in hemoglobin is unknown, but it does not appear to result from hemorrhage or hemolysis.

Hemoglobin must be measured prior to initiation of LETAIRIS and should be measured at one month and periodically thereafter. If a clinically significant decrease in hemoglobin is observed and other causes have been excluded, discontinuation of treatment should be considered.

5.3 Peripheral Edema

Peripheral edema is a known class effect of endothelin receptor antagonists, and is also a clinical consequence of PAH and worsening PAH. In the placebo-controlled studies, there was an increased incidence of peripheral edema in patients treated with doses of 5 or 10 mg LETAIRIS compared to placebo [see *Adverse Reactions (6)*]. Most edema was mild to moderate in severity. If clinically significant peripheral edema develops, with or without associated weight gain, further evaluation should be undertaken to determine the cause, such as heart failure, and the possible need for specific treatment.

5.4 Co-administration of LETAIRIS and Cyclosporine A

Cyclosporine is a strong inhibitor of P-glycoprotein (P-gp), Organic Anion Transport Protein (OATP), and CYP3A4. *In vitro* data indicate ambrisentan is a substrate of P-gp, OATP and CYP3A. Therefore, use caution when LETAIRIS is co-administered with cyclosporine A because cyclosporine A may cause increased exposure to LETAIRIS [see *Drug Interactions (7)*].

5.5 Co-administration of LETAIRIS and Strong CYP3A and 2C19 Inhibitors

Use caution when LETAIRIS is co-administered with strong CYP3A-inhibitors (e.g., ketoconazole) and CYP2C19-inhibitors (e.g., omeprazole) [see *Drug Interactions (7)*].

5.6 Prescribing and Distribution Program for LETAIRIS

Because of the risks of liver injury and birth defects, LETAIRIS is available only through a special restricted distribution program called the LETAIRIS Education and Access Program (LEAP). Only prescribers and pharmacies registered with LEAP may prescribe and distribute LETAIRIS. In addition, LETAIRIS may be dispensed only to patients who are enrolled in and meet all conditions of LEAP.

To enroll in LEAP, prescribers must complete the LEAP Prescriber Enrollment and Agreement Form indicating agreement to (see LEAP Prescriber Enrollment and Agreement Form for full prescribing physician agreement):

- Read the Prescribing Information (PI) and Medication Guide for LETAIRIS
- Enroll all patients in LEAP and re-enroll patients after the first 6 months of treatment and annually thereafter
- Review the LETAIRIS Medication Guide and patient education brochure(s) with every patient

- Educate patients on the risks of LETAIRIS, including the risks of hepatotoxicity and teratogenicity [see *Boxed Warning*]
- Educate and counsel women of childbearing potential to use two different forms of contraception including at least one primary form during LETAIRIS treatment and for one month following treatment discontinuation. If the patient has had a tubal sterilization or a Copper T 380A IUD or LNG 20 IUD inserted, no additional contraception is needed [see *Boxed Warning, Contraindication (4.1)*].

Primary forms of contraception include tubal sterilization, hormonal (combination oral contraceptives, transdermal patch, injectables, implantables, or vaginal ring), IUD, and a partner's vasectomy. A Copper T 380A IUD or LNG 20 IUD can be used alone, i.e. without a secondary form of contraception, as can tubal sterilization.

Secondary forms of contraception include barrier contraceptives such as latex condoms, diaphragms, and cervical caps.

- Order and review liver function tests (including aminotransferases and bilirubin) prior to initiation of LETAIRIS treatment and monthly during treatment
- For women of childbearing potential, order and review a pregnancy test prior to initiation of LETAIRIS treatment and monthly during treatment
- Counsel patients who fail to comply with the program requirements
- Notify LEAP of any adverse events, including liver injury, or if any patient becomes pregnant during LETAIRIS treatment

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Safety data for LETAIRIS were obtained from two 12-week, placebo-controlled studies in patients with PAH (ARIES-1 and ARIES-2) and four nonplacebo-controlled studies in 483 patients with PAH who were treated with doses of 1, 2.5, 5, or 10 mg once daily. The exposure to LETAIRIS in these studies ranged from 1 day to 4 years (N=418 for at least 6 months and N=343 for at least 1 year).

In ARIES-1 and ARIES-2, a total of 261 patients received LETAIRIS at doses of 2.5, 5, or 10 mg once daily and 132 patients received placebo. The adverse events that occurred in >3% of the patients receiving LETAIRIS and were more frequent on LETAIRIS than placebo are shown in Table 1.

Table 1 Adverse Events in >3% of PAH Patients Receiving LETAIRIS and More Frequent than Placebo

	Placebo (N=132)	LETAIRIS (N=261)	
Adverse event	n (%)	n (%)	Placebo-adjusted (%)
Peripheral edema	14 (11)	45 (17)	6
Nasal congestion	2 (2)	15 (6)	4
Sinusitis	0 (0)	8 (3)	3
Flushing	1 (1)	10 (4)	3
Palpitations	3 (2)	12 (5)	3
Nasopharyngitis	1 (1)	9 (3)	2
Abdominal pain	1 (1)	8 (3)	2
Constipation	2 (2)	10 (4)	2
Dyspnea	4 (3)	11 (4)	1
Headache	18 (14)	38 (15)	1

Note: This table includes all adverse events >3% incidence in the combined LETAIRIS treatment group and more frequent than in the placebo group, with a difference of $\geq 1\%$ between the LETAIRIS and placebo groups.

Most adverse drug reactions were mild to moderate and only nasal congestion was dose-dependent. Fewer patients receiving LETAIRIS had adverse events related to liver function tests compared to placebo.

Few notable differences in the incidence of adverse drug reactions were observed for patients by age or sex. Peripheral edema was similar in younger patients (<65 years) receiving LETAIRIS (14%; 29/205) or placebo (13%; 13/104), and was greater in elderly patients (≥ 65 years) receiving LETAIRIS (29%; 16/56) compared to placebo (4%; 1/28). The results of such subgroup analyses must be interpreted cautiously.

The incidence of treatment discontinuations due to adverse events other than those related to pulmonary hypertension during the clinical trials in patients with pulmonary arterial hypertension was similar for LETAIRIS (2%; 5/261 patients) and placebo (2%; 3/132 patients). The incidence of patients with serious adverse events other than those related to pulmonary hypertension during the clinical trials in patients with pulmonary arterial hypertension was similar for placebo (7%; 9/132 patients) and for LETAIRIS (5%; 13/261 patients).

7 DRUG INTERACTIONS

Studies with human liver tissue indicate that ambrisentan is metabolized by CYP3A4, CYP2C19, and uridine 5'-diphosphate glucuronosyltransferases (UGTs) 1A9S, 2B7S, and 1A3S. *In vitro* studies suggest that ambrisentan is a substrate of Organic Anion Transport Protein (OATP). *In vitro* studies show ambrisentan is a substrate but not an inhibitor of P-gp.

The drug interaction potential of ambrisentan is not well characterized because *in vivo* drug interaction studies were not conducted with the following types of drugs: strong inhibitors of CYP3A4 (atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin), and CYP2C19 (omeprazole), strong inducers of CYP3A and 2C19 (rifampin), strong inhibitors of the transporters P-gp (cyclosporine A) and OATP (cyclosporine A, rifampin); and inducers of CYPs, UGTs and P-gp (rifampin). The impact of co-administration of such drugs on ambrisentan exposure is therefore unknown.

7.1 Cyclosporine A

Use caution when LETAIRIS is co-administered with cyclosporine A (see Warnings and Precautions 5.4).

7.2 Strong CYP3A or 2C19 Inhibitors

Use caution when LETAIRIS is co-administered with strong CYP3A-inhibitors (e.g., ketoconazole) or CYP2C19-inhibitors (e.g., omeprazole) [see *Warnings and Precautions (5.5)*].

7.3 Inducers of P-gp, CYPs, and UGTs

Use caution when LETAIRIS is co-administered with inducers of P-gp, CYPs, and UGTs.

7.4 Warfarin

In healthy volunteers receiving warfarin, daily doses of LETAIRIS (10 mg once daily) did not have a clinically significant effect on prothrombin time (PT), International Normalized Ratio (INR), or the pharmacokinetics of S-warfarin (CYP2C9 substrate) or R-warfarin (CYP3A4 substrate).

In patients with PAH receiving warfarin-type anticoagulants, concomitant administration of LETAIRIS did not result in a clinically relevant change in PT, INR or anticoagulant dose. Therefore, no dose-adjustments for warfarin or LETAIRIS are required when co-administered.

7.5 Sildenafil

In healthy volunteers receiving a single dose of sildenafil (20 mg), daily doses of LETAIRIS (10 mg once daily) did not have a clinically relevant effect on the pharmacokinetics of sildenafil or the active metabolite, n-desmethyl sildenafil. Similarly, daily doses of sildenafil (20 mg tid) did not have a clinically relevant effect on the pharmacokinetics of a single dose of LETAIRIS (10 mg). Therefore, no dose-adjustments for sildenafil or LETAIRIS are required when co-administered.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X [see *Contraindications (4.1)*].

8.3 Nursing Mothers

It is not known whether ambrisentan is excreted in human milk. Breastfeeding while receiving LETAIRIS is not recommended. A preclinical study in rats has shown decreased survival of newborn pups (mid and high doses) and effects on testicle size and fertility of pups (high dose) following maternal treatment with ambrisentan from late gestation through weaning. Doses tested were 17x, 51x, and 170x (low, mid, high dose, respectively) the maximum oral human dose of 10 mg on a mg/mm² basis.

8.4 Pediatric Use

Safety and effectiveness of LETAIRIS in pediatric patients have not been established.

8.5 Geriatric Use

In the two placebo-controlled clinical studies of LETAIRIS, 21% of patients were ≥ 65 years old and 5% were ≥ 75 years old. The elderly (age ≥ 65 years) showed less improvement in walk distances with LETAIRIS than younger patients did, but the results of such subgroup analyses must be interpreted cautiously. Peripheral edema was more common in the elderly than in younger patients.

8.6 Renal Impairment

The impact of renal impairment on the pharmacokinetics of ambrisentan has been examined using a population pharmacokinetic approach in PAH patients with creatinine clearances ranging between 20 and 150 mL/min. There was no significant impact of mild or moderate renal impairment on exposure to ambrisentan [see *Clinical Pharmacology* (12.3)]. Dose adjustment of LETAIRIS in patients with mild or moderate renal impairment is therefore not required. There is no information on the exposure to ambrisentan in patients with severe renal impairment.

The impact of hemodialysis on the disposition of ambrisentan has not been investigated.

8.7 Hepatic Impairment

The influence of pre-existing hepatic impairment on the pharmacokinetics of ambrisentan has not been evaluated. Because there is *in vitro* and *in vivo* evidence of significant metabolic and biliary contribution to the elimination of ambrisentan, hepatic impairment would be expected to have significant effects on the pharmacokinetics of ambrisentan [see *Clinical Pharmacology* (12.3)]. LETAIRIS is not recommended in patients with moderate or severe hepatic impairment. Use caution when administering LETAIRIS to patients with mild pre-existing impaired liver function who may require reduced doses of LETAIRIS [see *Dosage and Administration* (2.3)].

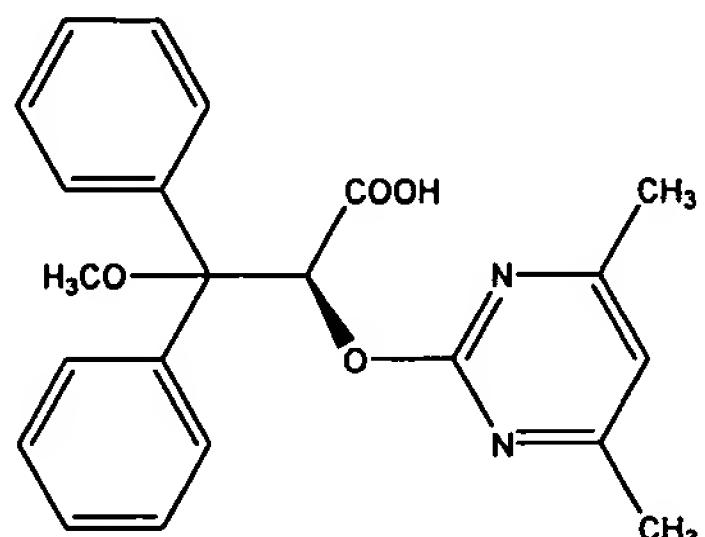
10 OVERDOSAGE

There is no experience with overdosage of LETAIRIS. The highest single dose of LETAIRIS administered to healthy volunteers was 100 mg and the highest daily dose administered to patients with PAH was 10 mg once daily. Massive overdosage could potentially result in hypotension that may require intervention.

11 DESCRIPTION

LETAIRIS is the brand name for ambrisentan, an endothelin receptor antagonist that is selective for the endothelin type-A (ET_A) receptor. The chemical name of ambrisentan is (+)-(2S)-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic acid. It has a molecular formula of C₂₂H₂₂N₂O₄ and a molecular weight of 378.42. It contains a single chiral center determined to be the (S) configuration and has the following structural formula:

Figure 1 Ambrisentan Structural Formula



Ambrisentan is a white to off-white, crystalline solid. It is a carboxylic acid with a pKa of 4.0. Ambrisentan is practically insoluble in water and in aqueous solutions at low pH. Solubility increases in aqueous solutions at higher pH. In the solid state ambrisentan is very stable, is not hygroscopic, and is not light sensitive.

LETAIRIS is available as 5 mg and 10 mg film-coated tablets for once-daily oral administration. The tablets include the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate and microcrystalline cellulose. The tablets are film-coated with a coating material containing FD&C Red #40 aluminum lake, lecithin, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. Each square, pale pink LETAIRIS tablet contains 5 mg of ambrisentan. Each oval, deep pink LETAIRIS tablet contains 10 mg of ambrisentan. LETAIRIS tablets are unscored.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Endothelin-1 (ET-1) is a potent autocrine and paracrine peptide. Two receptor subtypes, ET_A and ET_B, mediate the effects of ET-1 in the vascular smooth muscle and endothelium. The primary actions of ET_A are vasoconstriction and cell proliferation, while the predominant actions of ET_B are vasodilation, antiproliferation, and ET-1 clearance.

In patients with PAH, plasma ET-1 concentrations are increased as much as 10-fold and correlate with increased mean right atrial pressure and disease severity. ET-1 and ET-1 mRNA concentrations are increased as much as 9-fold in the lung tissue of patients with PAH, primarily in the endothelium of pulmonary arteries. These findings suggest that ET-1 may play a critical role in the pathogenesis and progression of PAH.

Ambrisentan is a high affinity ($K_i=0.011$ nM) ET_A receptor antagonist with a high selectivity for the ET_A versus ET_B receptor (>4000-fold). The clinical impact of high selectivity for ET_A is not known.

12.2 Pharmacodynamics

Cardiac Electrophysiology

In a randomized, positive- and placebo-controlled, parallel-group study, healthy subjects received either LETAIRIS 10 mg daily followed by a single dose of 40 mg, placebo followed by a single dose of moxifloxacin 400 mg, or placebo alone. LETAIRIS 10 mg daily had no significant effect on the QTc interval. The 40 mg dose of LETAIRIS increased mean QTc at t_{max} by 5 ms with an upper 95% confidence limit of 9 ms. For patients receiving LETAIRIS 5-10 mg daily and not taking metabolic inhibitors, no significant QT prolongation is expected.

12.3 Pharmacokinetics

The absolute bioavailability of ambrisentan is not known. Ambrisentan is rapidly absorbed with peak concentrations occurring approximately 2 hours after oral administration in healthy subjects and PAH patients. Food does not affect its bioavailability. *In vitro* studies indicate that ambrisentan is a substrate of P-gp. Ambrisentan is highly bound to plasma proteins (99%). The elimination of ambrisentan is predominantly by non-renal pathways, but the relative contributions of metabolism and biliary elimination have not been well characterized. Based on *in vitro* data, interactions with strong inhibitors of P glycoprotein (P-gp), the Organic Anion Transport Protein (OATP), CYP3A4, CYP2C19, and uridine 5' diphosphate glucuronosyltransferases (UGTs) are possible [see *Drug Interactions* (7)]. The mean oral clearance of ambrisentan is 38 mL/min and 19 mL/min in healthy subjects and in PAH patients, respectively. Although ambrisentan has a 15-hour terminal half-life, the mean trough concentration of ambrisentan at steady-state is about 15% of the mean peak concentration and the accumulation factor is about 1.2 after long-term daily dosing, indicating that the effective half-life of ambrisentan is about 9 hours.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Oral carcinogenicity studies of up to two years duration were conducted at starting doses of 10, 30, and 60 mg/kg/day in rats (8 to 48 times the maximum recommended human dose [MRHD] on a mg/m² basis) and at 50, 150 and 250 mg/kg/day in mice (28 to 140 times the MRHD). In the rat study, the high and mid-dose male and female groups had their doses lowered to 40 and 20 mg/kg/day, respectively, in week 51 because of effects on survival. The high dose males and females were taken off drug completely in weeks 69 and 93, respectively. The only evidence of ambrisentan-related carcinogenicity was a positive trend in male rats, for the combined incidence of benign basal cell tumor and basal cell carcinoma of skin/subcutis in the mid-dose group (high-dose group excluded from analysis), and the occurrence of mammary fibroadenomas in males in the high-dose group. In the mouse study, high dose male and female groups had their doses lowered to 150 mg/kg/day in week 39 and were

taken off drug completely in week 96 (males) or week 76 (females). In mice, ambrisentan was not associated with excess tumors in any dosed group.

Positive findings of clastogenicity were detected, at drug concentrations producing moderate to high toxicity, in the chromosome aberration assay in cultured human lymphocytes. There was no evidence for genetic toxicity of ambrisentan when tested *in vitro* in bacteria (Ames test) or *in vivo* in rats (micronucleus assay, unscheduled DNA synthesis assay).

The development of testicular tubular atrophy and impaired fertility has been linked to the chronic administration of endothelin receptor antagonists in rodents. Testicular tubular degeneration was observed in rats treated with ambrisentan for two years at doses \geq 10 mg/kg/day (8-fold MRHD). Increased incidences of testicular findings were also observed in mice treated for two years at doses \geq 50 mg/kg/day (28-fold MRHD). Effects on sperm count, sperm morphology, mating performance and fertility were observed in fertility studies in which male rats were treated with ambrisentan at oral doses of 300 mg/kg/day (236-fold MRHD). At doses of \geq 10 mg/kg/day, observations of testicular histopathology in the absence of fertility and sperm effects were also present. There are insufficient data on the effects of ambrisentan or other endothelin receptor antagonists on testicular function in man.

14 CLINICAL STUDIES

14.1 Pulmonary Arterial Hypertension (PAH)

Two 12-week, randomized, double-blind, placebo-controlled, multicenter studies were conducted in 393 patients with PAH (WHO Group 1). The two studies were identical in design except for the doses of LETAIRIS and the geographic region of the investigational sites. ARIES-1 compared once-daily doses of 5 mg and 10 mg LETAIRIS to placebo, while ARIES-2 compared once-daily doses of 2.5 mg and 5 mg LETAIRIS to placebo. In both studies, LETAIRIS or placebo was added to current therapy, which could have included a combination of anticoagulants, diuretics, calcium channel blockers, or digoxin, but not epoprostenol, treprostинil, iloprost, bosentan, or sildenafil. The primary study endpoint was 6-minute walk distance. In addition, clinical worsening, WHO functional class, dyspnea, and SF-36[®] Health Survey were assessed.

Patients had idiopathic PAH (64%) or PAH associated with connective tissue disease (32%), HIV infection (3%), or anorexigen use (1%). There were no patients with PAH associated with congenital heart disease.

Patients had WHO functional class I (2%), II (38%), III (55%), or IV (5%) symptoms at baseline. The mean age of patients was 50 years, 79% of patients were female, and 77% were Caucasian.

Submaximal Exercise Capacity

Results of the 6-minute walk distance at 12 weeks for the ARIES-1 and ARIES-2 studies are shown in Table 2 and Figure 2.

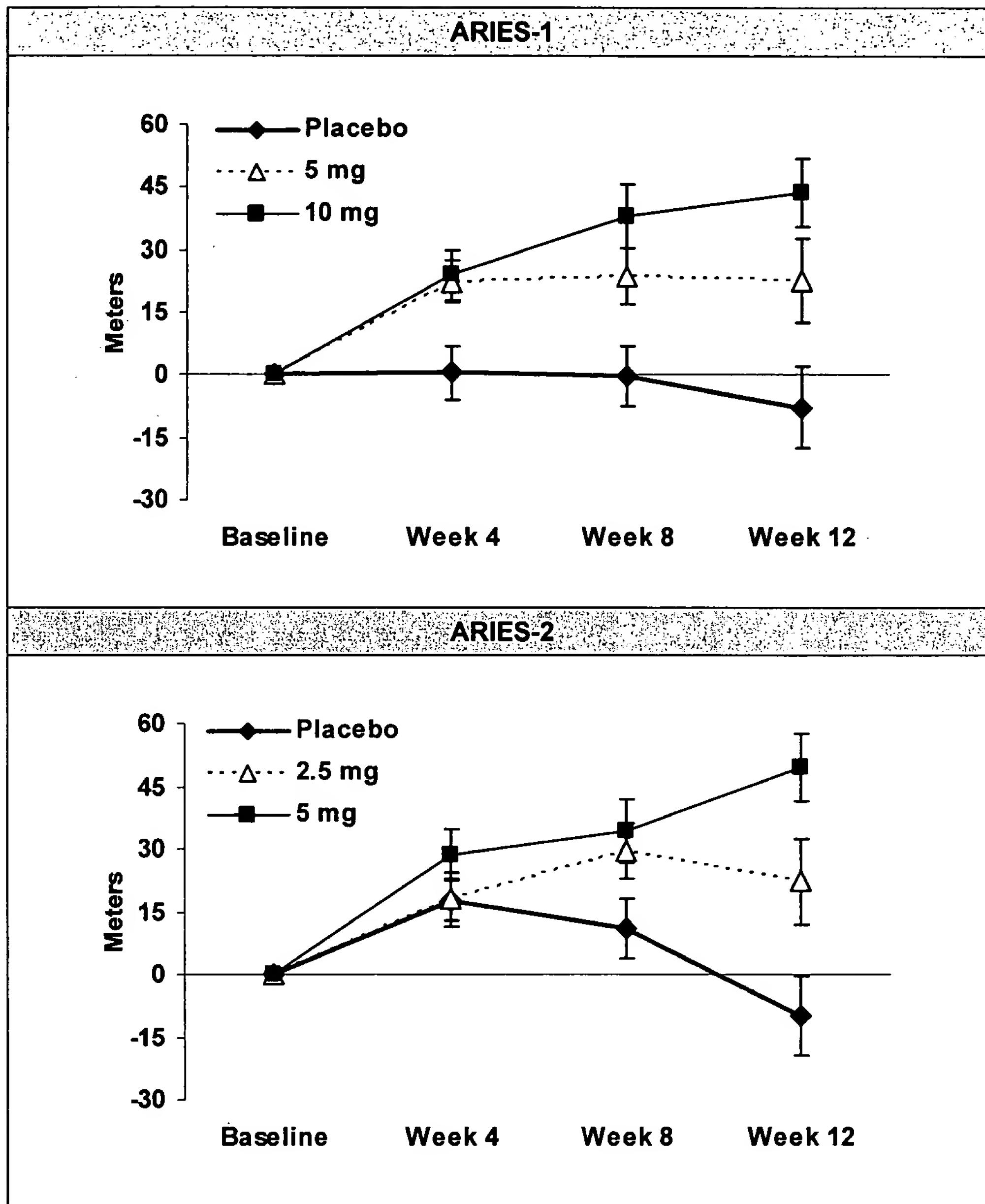
Table 2 Changes from Baseline in 6-Minute Walk Distance (meters)

	ARIES-1			ARIES-2		
	Placebo (N=67)	5 mg (N=67)	10 mg (N=67)	Placebo (N=65)	2.5 mg (N=64)	5 mg (N=63)
Baseline	342 ± 73	340± 77	342 ± 78	343 ± 86	347± 84	355 ± 84
Mean change from baseline	-8 ± 79	23 ± 83	44 ± 63	-10 ± 94	22 ± 83	49 ± 75
Placebo-adjusted mean change from baseline		31	51		32	59
Placebo-adjusted median change from baseline		27	39		30	45
p-value†		0.008	<0.001		0.022	<0.001

Mean ± standard deviation

† p-values are Wilcoxon rank sum test comparisons of LETAIRIS to placebo at Week 12 stratified by idiopathic PAH and non-idiopathic PAH patients

Figure 2 Mean Change in 6-minute Walk Distance



Mean change from baseline in 6-minute walk distance in the placebo and LETAIRIS groups
Values are expressed as mean \pm standard error of the mean.

In both studies, treatment with LETAIRIS resulted in a significant improvement in 6-minute walk distance for each dose of LETAIRIS and the improvements increased with dose. An increase in 6-minute walk distance was observed after 4 weeks of treatment with LETAIRIS, with a dose-response observed after 12 weeks of treatment. Improvements in walk distance with LETAIRIS were smaller for elderly patients (age ≥ 65) than younger patients and for patients with secondary PAH than for patients

with idiopathic PAH. The results of such subgroup analyses must be interpreted cautiously.

The effects of LETAIRIS on walk distances at trough drug levels are not known. Because only once daily dosing was studied in the clinical trials, the efficacy and safety of more frequent dosing regimens for LETAIRIS are not known. If exercise capacity is not sustained throughout the day in a patient, consider other PAH treatments that have been studied with more frequent dosing regimens.

Clinical Worsening

Time to clinical worsening of PAH was defined as the first occurrence of death, lung transplantation, hospitalization for PAH, atrial septostomy, study withdrawal due to the addition of other PAH therapeutic agents or study withdrawal due to early escape. Early escape was defined as meeting two or more of the following criteria: a 20% decrease in the 6-minute walk distance; an increase in WHO functional class; worsening right ventricular failure; rapidly progressing cardiogenic, hepatic, or renal failure; or refractory systolic hypotension. The clinical worsening events during the 12-week treatment period of the LETAIRIS clinical trials are shown in Table 3 and Figure 3.

Table 3 Time to Clinical Worsening

	ARIES-1		ARIES-2	
	Placebo (N=67)	LETAIRIS (N=134)	Placebo (N=65)	LETAIRIS (N=127)
Clinical worsening, no. (%)	7 (10%)	4 (3%)	13 (22%)	8 (6%)
Hazard ratio		0.28		0.30
p-value, Fisher exact test		0.044		0.006
p-value, Log-rank test		0.030		0.005

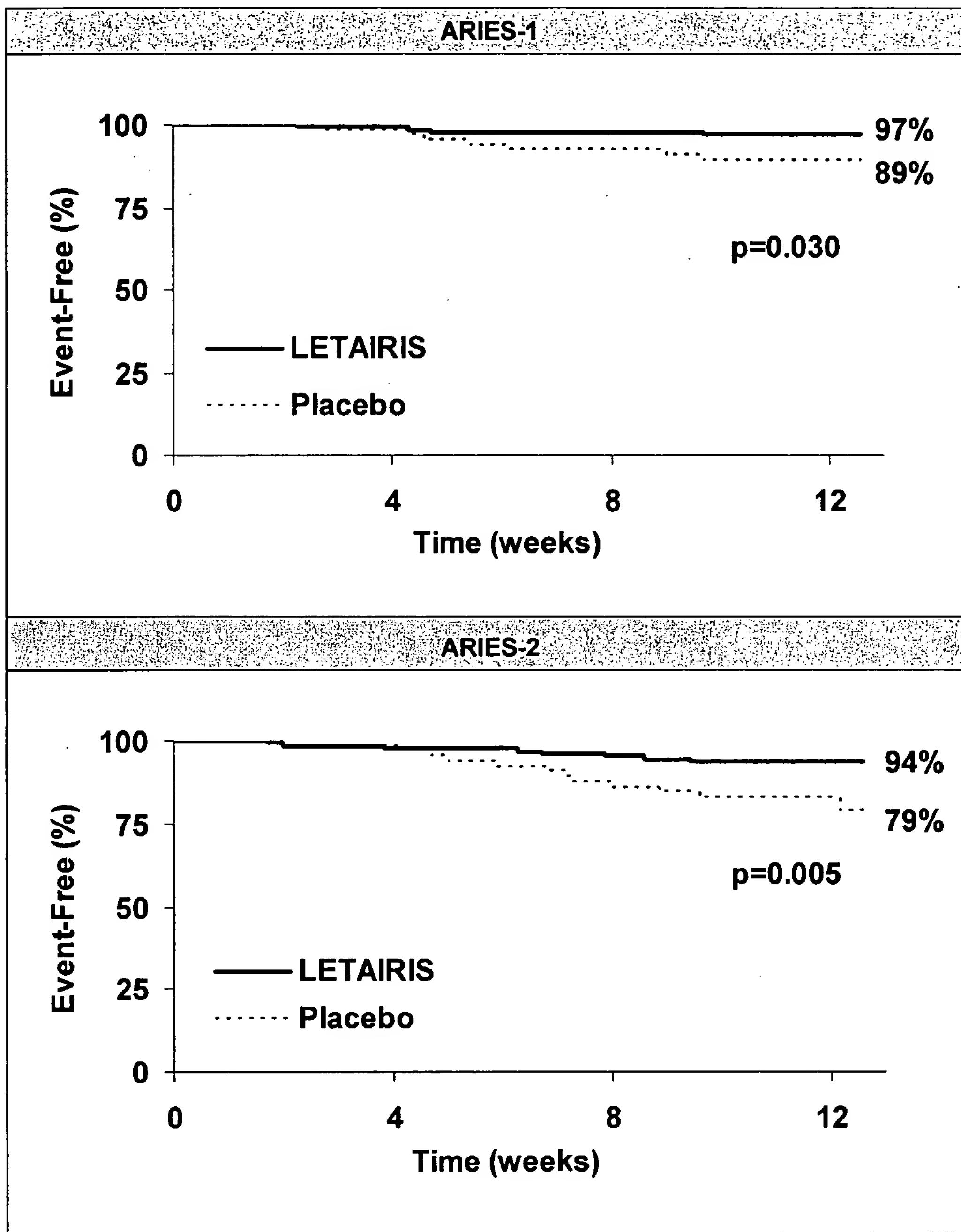
Intention-to-treat population

Note: Patients may have had more than one reason for clinical worsening.

Nominal p-values

There was a significant delay in the time to clinical worsening for patients receiving LETAIRIS compared to placebo. Results in subgroups such as the elderly were also favorable.

Figure 3 Time to Clinical Worsening



Time from randomization to clinical worsening with Kaplan-Meier estimates of the proportions of failures in ARIES-1 and ARIES-2.

p-values shown are the log-rank comparisons of LETAIRIS to placebo stratified by idiopathic PAH and non-idiopathic PAH patients

14.2 Long-term Treatment of PAH

The long-term follow-up of the patients who were treated with LETAIRIS in the two pivotal studies and their open-label extension (N=383) shows that 95% were still alive at one year and 94% were still receiving LETAIRIS monotherapy. These uncontrolled observations do not allow comparison with a group not given LETAIRIS and cannot be used to determine the long-term effect of LETAIRIS.

14.3 Use in Patients with Prior Endothelin Receptor Antagonist (ERA) Related Liver Function Abnormalities

In an uncontrolled, open-label study, 36 patients who had previously discontinued endothelin receptor antagonists (ERAs: bosentan, an investigational drug, or both) due to aminotransferase elevations >3 x upper limit of normal (ULN) were treated with LETAIRIS. Prior elevations were predominantly moderate, with 64% of the ALT elevations <5 x ULN, but 9 patients had elevations >8 x ULN. Eight patients had been re-challenged with bosentan and/or the investigational ERA and all eight had a recurrence of aminotransferase abnormalities that required discontinuation of ERA therapy. All patients had to have normal aminotransferase levels on entry to this study. Twenty-five of the 36 patients were also receiving prostanoid and/or phosphodiesterase type 5 (PDE5) inhibitor therapy. Two patients discontinued early (including one of the patients with a prior 8 x ULN elevation). Of the remaining 34 patients, one patient experienced a mild aminotransferase elevation at 12 weeks on LETAIRIS 5 mg that resolved with decreasing the dosage to 2.5 mg, and that did not recur with later escalations to 10 mg. With a median follow-up of 13 months and with 50% of patients increasing the dose of LETAIRIS to 10 mg, no patients were discontinued for aminotransferase elevations. While the uncontrolled study design does not provide information about what would have occurred with re-administration of previously used ERAs or show that LETAIRIS led to fewer aminotransferase elevations than would have been seen with those drugs, the study indicates that LETAIRIS may be tried in patients who have experienced asymptomatic aminotransferase elevations on other ERAs after aminotransferase levels have returned to normal.

16 HOW SUPPLIED/STORAGE AND HANDLING

Because of the risk of liver injury and birth defects, LETAIRIS may be prescribed only through the LETAIRIS Education and Access Program (LEAP) by calling 1-866-664-LEAP (5327) or by logging on to www.letairis.com. Adverse events can also be reported directly via this number.

LETAIRIS film-coated, unscored tablets are supplied as follows:

Package Configuration	Tablet Strength	NDC No.	Description of Tablet; Debossed on Tablet; Size
30 count blister	5 mg	61958-0801-2	Square convex, pale pink; "5" on side 1 and "GSI" on side 2; 6.6 mm Square
30 count blister	10 mg	61958-0802-2	Oval convex; deep pink; "10" on side 1 and "GSI" on side 2; 9.8 mm x 4.9 mm Oval

R only

Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F) [see *USP controlled room temperature*]. Store LETAIRIS in its original packaging.

17 PATIENT COUNSELING INFORMATION

As a part of patient counseling, doctors must review the LETAIRIS Medication Guide with every patient [see *FDA-Approved Medication Guide (17.5)*].

17.1 Importance of Preventing Pregnancy

Patients should be advised that LETAIRIS may cause fetal harm. LETAIRIS treatment should only be initiated in women of childbearing potential following a negative pregnancy test. Women of childbearing potential should be informed of the importance of monthly pregnancy tests and the need to use two different forms of contraception including at least one primary form simultaneously during LETAIRIS treatment and for one month following treatment discontinuation. Primary forms of contraception other than tubal sterilization include hormonal (combination oral contraceptives, transdermal patch, injectables, implantables, or vaginal ring), IUD, and a partner's vasectomy. A Copper T 380A IUD or LNG 20 IUD can be used alone, i.e. without a secondary form of contraception, as can tubal sterilization. Patients should be instructed to immediately contact their physician if they suspect they may be pregnant [see *Prescribing and Distribution Program for LETAIRIS (5.5)*].

17.2 Adverse Liver Effects

Patients should be advised of the importance of monthly liver function testing and instructed to immediately report any symptoms of potential liver injury (such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant abdominal discomfort, jaundice, dark urine or itching) to their physician.

17.3 Hematological Change

Patients should be advised of the importance of hemoglobin testing.

17.4 Administration

Patients should be advised not to split, crush, or chew tablets.

17.5 FDA-Approved Medication Guide

*Sections or subsections omitted from the full prescribing information are not listed.

Gilead Sciences, Inc., Foster City, CA 94404

June 2007

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GS22-081-000

**Medication Guide
LETAIRIS™ (le-TAIR-is)
Tablets
(ambrisentan)**

Read this Medication Guide before you start taking LETAIRIS and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about LETAIRIS?

• Possible liver injury.

LETAIRIS can cause liver injury. You must have a blood test to check your liver function before you start LETAIRIS and each month after that. Your doctor will order these blood tests. (See "What are the possible side effects of LETAIRIS?" for information about the signs of liver problems.) **Tell your doctor if you have had moderate or severe liver problems, including liver problems while taking other medicines.**

• Serious birth defects.

LETAIRIS can cause serious birth defects if taken during pregnancy. Women must not be pregnant when they start taking LETAIRIS or become pregnant during treatment. Women who are able to get pregnant must have a negative pregnancy test before beginning treatment with LETAIRIS and each month during treatment. Your doctor will decide when to do the test, depending on your menstrual cycle.

Women who are able to get pregnant must use two different reliable forms of birth control at the same time, during LETAIRIS treatment and for one month after stopping LETAIRIS. Talk with your doctor or gynecologist (a doctor who specializes in female reproduction) to find out about how to prevent pregnancy. **Do not have unprotected sex. Tell your doctor right away if you miss a menstrual period or think you may be pregnant.**

LETAIRIS is available only through a restricted program called the LETAIRIS Education and Access Program (LEAP). To receive LETAIRIS, you must talk to your doctor, understand the benefits and risks of LETAIRIS, and agree to all of the instructions in the LEAP program.

What is LETAIRIS?

LETAIRIS is a prescription medicine to treat pulmonary arterial hypertension (PAH), which is high blood pressure in the arteries of your lungs.

LETAIRIS can improve your ability to exercise and it can help slow down the worsening of your physical condition and symptoms.

Who should not take LETAIRIS?

Do not take LETAIRIS if:

- you are pregnant, plan to become pregnant, or become pregnant during treatment with LETAIRIS. LETAIRIS can cause serious birth defects.** (See "What is the most important information I should know about LETAIRIS?") Serious birth defects from LETAIRIS happen early in pregnancy.
- your blood tests show possible liver injury.**

Tell your doctor about all your medical conditions and all the medicines you take including prescription and nonprescription medicines. LETAIRIS and other medicines may affect each other causing side effects. Do not start any new medicines until you check with your doctor.

LETAIRIS has not been studied in children.

How should I take LETAIRIS?

LETAIRIS will be mailed to you by a specialty pharmacy. Your doctor will give you complete details.

- Take LETAIRIS exactly as your doctor tells you. Do not stop taking LETAIRIS unless your doctor tells you.
- You can take LETAIRIS with or without food.
- Do not split, crush or chew LETAIRIS tablets.
- It will be easier to remember to take LETAIRIS if you take it at the same time each day.
- If you take more than your regular dose of LETAIRIS, call your doctor right away.
- If you miss a dose, take it as soon as you remember that day. Take your next dose at the regular time. Do not take two doses at the same time to make up for a missed dose.
- During treatment your doctor will test your blood for signs of side effects to your liver and red blood cells.

What should I avoid while taking LETAIRIS?

- **Do not get pregnant** while taking LETAIRIS. (See the serious birth defects section of "What is the most important information I should know about LETAIRIS?") If you miss a menstrual period, or think you might be pregnant, call your doctor right away.
- **Breastfeeding is not recommended** while taking LETAIRIS. It is not known if LETAIRIS can pass through your milk and harm your baby.

What are the possible side effects of LETAIRIS?

Serious side effects of LETAIRIS include:

- **Possible liver injury.** (See "What is the most important information I should know about LETAIRIS?") Call your doctor right away if you have any of these symptoms of liver problems: loss of appetite, nausea, vomiting, fever, unusual tiredness, right upper stomach pain, yellowing of the skin or the whites of your eyes (jaundice), dark urine, or itching.
- **Serious birth defects.** (See "What is the most important information I should know about LETAIRIS?")
- **Low sperm count.** LETAIRIS can lower sperm count in animals. If this happens in men, they may lose the ability to father children. Talk with your doctor if you have any questions or concerns.

The most common side effects of LETAIRIS are:

- Lowering of red blood cell count
- Swelling of legs and ankles (edema)
- Stuffy nose (nasal congestion)
- Inflamed nasal passages (sinusitis)
- Hot flashes or getting red in the face (flushing)
- Feeling your heart beat (palpitations)
- Red and sore throat and nose
- Stomach pain
- Constipation
- Shortness of breath
- Headache

How should I store LETAIRIS?

Store LETAIRIS at less than 86 °F (30 °C), in the package it comes in.

General information about LETAIRIS

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you have any concerns or questions about LETAIRIS, ask your doctor or other healthcare provider. This Medication Guide is only a summary of some important information about LETAIRIS. Your doctor can give you information about LETAIRIS that was written for healthcare professionals. Do not use LETAIRIS

for any condition other than that for which it was prescribed. Do not share LETAIRIS with other people. It may harm them.

Call 1-866-664-LEAP (5327) or visit www.letairis.com or www.gilead.com for more information.

What are the ingredients in LETAIRIS?

Active ingredient: ambrisentan

Inactive Ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate and microcrystalline cellulose. The tablets are film-coated with a coating material containing FD&C Red #40 aluminum lake, lecithin, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

This medication guide has been approved by the U.S. Food and Drug Administration.

Gilead Sciences, Inc., Foster City, CA 94404

June 2007

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GS22-081-000

EXHIBIT

F



US005703017A

United States Patent

[19]

Baumann et al.

[11] Patent Number: **5,703,017**[45] Date of Patent: **Dec. 30, 1997**

[54] **3-(HET) ARYLCARBOXYLIC ACID DERIVATIVES, THEIR PREPARATION AND INTERMEDIATES FOR THEIR PREPARATION**

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 409 368 1/1991 European Pat. Off. .
 481 512 4/1992 European Pat. Off. .
 517 215 12/1992 European Pat. Off. .
 548 710 6/1993 European Pat. Off. .

[75] Inventors: **Ernst Baumann, Dudenhofen; Joachim Rheinheimer; Uwe Josef Vogelbacher, both of Ludwigshafen; Matthias Bratz, Speyer; Hans Theobald; Matthias Gerber, both of Limburgerhof; Karl-Otto Westphalen, Speyer; Helmut Walter, Obrigheim; Wilhelm Rademacher, Limburgerhof, all of Germany**

[73] Assignee: **BASF Aktiengesellschaft, Ludwigshafen, Germany**

[21] Appl. No.: **537,843**

[22] PCT Filed: **Apr. 13, 1994**

[86] PCT No.: **PCT/EP94/01141**

§ 371 Date: **Oct. 19, 1995**

§ 102(e) Date: **Oct. 19, 1995**

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PCT Pub. Date: **Nov. 10, 1994**

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[51] Int. Cl.⁶ A01N 43/54; A01N 43/66; C07D 239/60; C07D 251/30; C07D 409/12; C07D 401/12; C07D 405/12; C07C 69/734

[52] U.S. Cl. 504/227; 504/228; 504/230; 504/239; 504/240; 504/241; 504/242; 504/243; 544/219; 544/235; 544/242; 544/253; 544/319; 546/340; 546/341; 548/204; 548/248; 548/341.5; 548/376.1; 549/79; 549/498; 549/499; 562/426; 562/470; 568/41; 568/425; 568/496

[58] Field of Search 504/227, 228, 504/230, 239, 240, 241, 242, 243; 544/219, 235, 253, 319, 242; 546/340, 341; 548/204, 248, 341.5, 376.1; 549/79, 498, 499; 562/426, 470; 568/41, 425, 496

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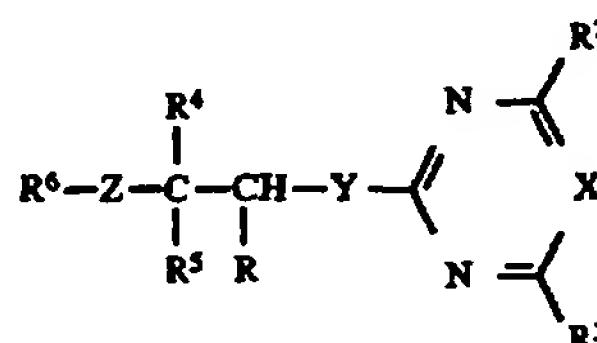
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Primary Examiner—S. Mark Clardy
 Attorney, Agent, or Firm—Keil & Weinkauf

[57] **ABSTRACT**

3-(HET)arylcrylic acid derivatives of the formula I



where R is formyl, CO₂H or a radical hydrolyzable to COOH and the other substituents have the following meanings:

R² and R³ are each halogen, alkyl, haloalkyl, alkoxy, haloalkoxy or alkylthio;

X is nitrogen or CR¹⁴, where R¹⁴ is hydrogen or, together with R³, forms an alkylene or alkenylene chain, in each of which a methylene group is replaced by oxygen;

R⁴ is phenyl or naphthyl, each of which is unsubstituted or substituted or an unsubstituted or substituted five-membered or six-membered heteroaromatic structure containing one to three nitrogen atoms or one sulfur or oxygen atom;

R⁵ is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, haloalkyl, alkoxyalkyl, alkylthioalkyl or phenyl;

R⁶ is C₁-C₈-alkyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl or C₃-C₄-cyclo-alkyl, each of which may be mono- or polysubstituted;

Y is sulfur, oxygen or a single bond; and

Z is sulfur or oxygen;

with the proviso that R⁶ is not unsubstituted C₁-C₄-alkyl when R⁴ is unsubstituted phenyl, Z is oxygen and simultaneously R⁵ is methyl or hydrogen.

14 Claims, No Drawings

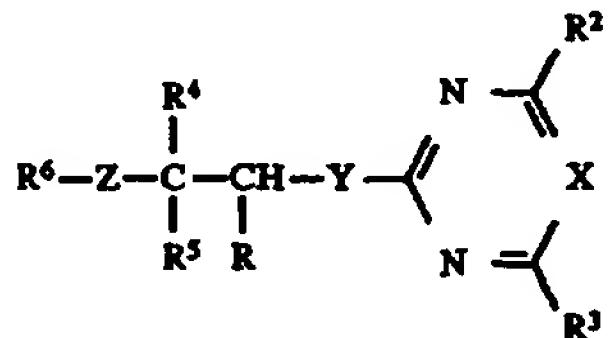
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3-(HET) ARYLCARBOXYLIC ACID DERIVATIVES, THEIR PREPARATION AND INTERMEDIATES FOR THEIR PREPARATION

This application has been filed under 35 USC 371 as a national stage application of PCT/EP94/01141, filed Apr. 13, 1994.

BACKGROUND OF THE INVENTION

3-(het)arylcarboxylic acid derivatives of the general formula I



where R is formyl, CO₂H or a radical hydrolyzable to COOH, and the other substituents have the following meanings:

R² is halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy or C₁-C₄-alkylthio;

X is nitrogen or CR¹⁴, where R¹⁴ is hydrogen or, together with R³, forms a 3-membered or 4-membered alkylene or alkenylene chain, in each of which a methylene group is replaced by oxygen;

R³ is halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy or C₁-C₄-alkylthio or R³ is linked to R¹⁴ as stated above to form a 5-membered or 6-membered ring;

R⁴ is phenyl or naphthyl which may be substituted by one or more, in particular one to three of the following radicals: halogen, nitro, cyano, hydroxyl, mercapto, amino, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₁-C₄-alkylthio, C₁-C₄-alkylamino, di-C₁-C₄-alkylamino, C₁-C₄-alkylcarbonyl or C₁-C₄-alkoxycarbonyl;

a five-membered or six-membered heteroaromatic structure which contains one to three nitrogen atoms and/or one sulfur or oxygen atom and may carry one or more of the following radicals: halogen, nitro, cyano, hydroxyl, mercapto, amino, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₁-C₄-alkylthio, C₁-C₄-alkylamino, C₁-C₄-dialkylamino, C₁-C₄-alkylcarbonyl, C₁-C₄-alkoxycarbonyl or phenyl;

R⁵ is hydrogen, C₁-C₄-alkyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl, C₃-C₈-cycloalkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxyalkyl, C₁-C₄-alkylthioalkyl or phenyl;

R⁶ is C₁-C₈-alkyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl or C₃-C₈-cycloalkyl, it being possible for these radicals to be mono- or polysubstituted in each case by: halogen, nitro, cyano, C₁-C₄-alkoxy, C₃-C₆-alkenyl, C₃-C₆-alkynyl, C₁-C₄-alkylthio, C₁-C₄-haloalkoxy, C₁-C₄-alkylcarbonyl, C₁-C₄-alkoxycarbonyl, C₁-C₄-alkylamino, di-C₁-C₄-alkylamino, phenyl or phenyl or phenoxy which is mono- or polysubstituted; for example mono- to trisubstituted, by halogen, nitro, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy or C₁-C₄-alkylthio;

Y is sulfur or oxygen or a single bond; and

Z is sulfur or oxygen;

with the proviso that R⁶ is not unsubstituted C₁-C₄-alkyl when R⁴ is unsubstituted phenyl, Z is oxygen and simultaneously R⁵ is methyl or hydrogen.

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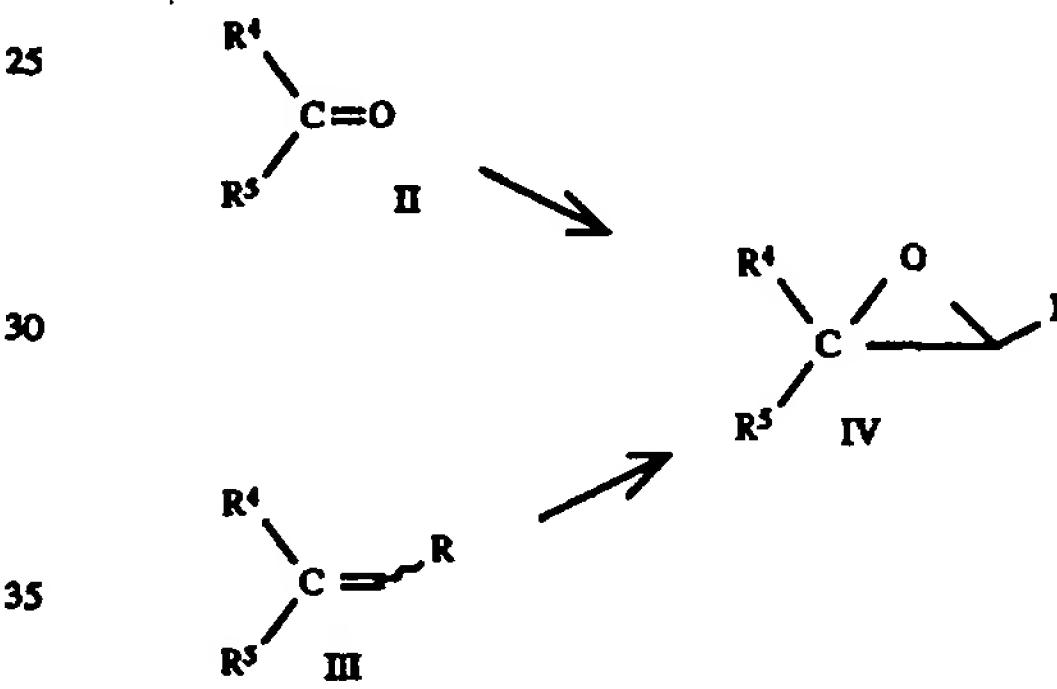
The prior art, e.g. EP-A 347 811, EP-A 400 741, EP-A 409 368, EP-A 481 512, EP-A 517 215, Chemical Abstracts, 119, No. 139 254c (1993), and the prior German application P 41 42 570 (EP-A-548 710), describes similar carboxylic acid derivatives, including 3-alkoxy derivatives but not those which carry a het(aryl) radical in the 3 position.

SUMMARY OF THE INVENTION

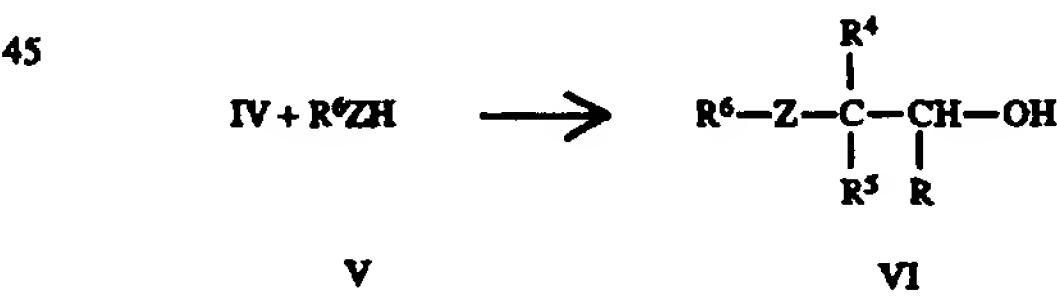
Since the herbicidal and/or bioregulatory action and selectivity of the known compounds is not always satisfactory, it is an object of the present invention to provide compounds having better selectivity and/or better biological activity.

We have found that this object is achieved and that the 3-(het)arylcarboxylic acid derivatives defined at the outset have excellent herbicidal and plant growth-regulating properties. Furthermore, the compounds I have good pharmacological efficacy, particularly in the cardiovascular sector.

The preparation of the novel compounds starts from the epoxides IV, which are obtained in a generally known manner, as described, for example, in J. March, Advanced Organic Chemistry, 2nd ed., 1983, page 862 and page 750, from the aldehydes or ketones II or the olefins III:



3-(Het)arylcarboxylic acid derivatives of the general formula VI can be prepared by reacting the epoxide of the general formula IV (for example, with R=ROOR¹⁰) with alcohols or thiols of the general formula V, where R⁶ and Z have the meanings stated in claim 1.



For this purpose, compounds of the general formula IV are heated with an excess of the compounds of the formula V, for example with 1.2-7, preferably 2-5, mole equivalents, to 50°-200° C., preferably 80°-150° C.

The reaction can also be carried out in the presence of a diluent. All solvents which are inert to the reagents used may be employed for this purpose.

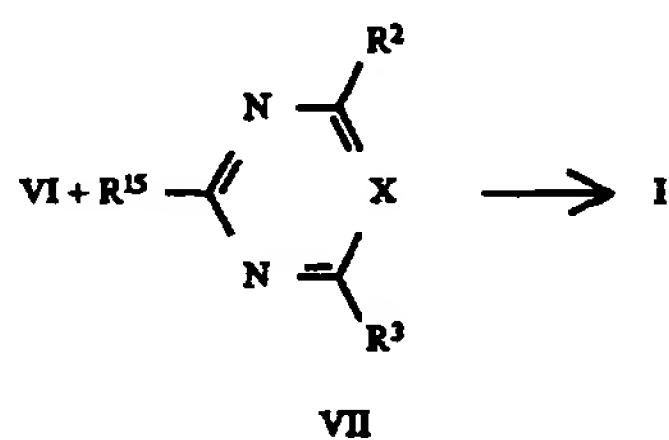
Examples of such solvents or diluents are water, aliphatic, alicyclic and aromatic hydrocarbons, each of which may be chlorinated, for example hexane, cyclohexane, petroleum ether, naphtha, benzene, toluene, xylene, methylene chloride, chloroform, carbon tetrachloride, ethylene chloride and trichloroethylene, ethers, such as diisopropyl ether, dibutyl ether, propylene oxide, dioxane and tetrahydrofuran, ketones, for example acetone, methyl ethyl ketone, methyl isopropyl ketone and methyl isobutyl ketone, nitriles, such

as acetonitrile and propionitrile, alcohols, such as methanol, ethanol, isopropanol, butanol and ethylene glycol, esters, for example ethyl acetate and amyl acetate, amides, such as dimethylformamide and dimethylacetamide, sulfoxides and sulfones, for example dimethyl sulfoxide and sulfolane, and bases, such as pyridine.

The reaction is preferably carried out at from 0° C. to the boiling point of the solvent or solvent mixture.

The presence of a catalyst for the reaction may be advantageous. Suitable catalysts are strong organic and inorganic acids and Lewis acids. Examples of these include sulfuric acid, hydrochloric acid, trifluoroacetic acid, boron trichloride etherate and titanium(IV) alcoholates.

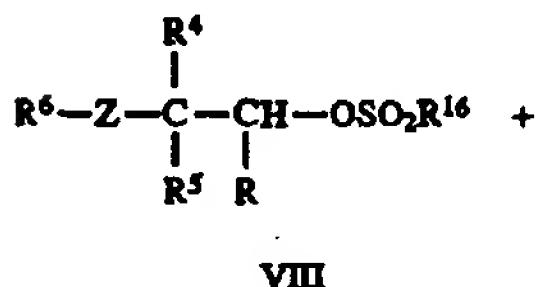
The novel compounds in which Y is oxygen and the remaining substituents have the meanings stated under the general formula I can be prepared, for example, by reacting the 3-(het)arylcarboxylic acid derivatives of the general formula VI in which the substituents have the stated meanings with compounds of the general formula VII



where R^{15} is halogen or $\text{R}^{16}-\text{SO}_2-$ and R^{16} may be C_1-C_4 -alkyl, C_1-C_4 -haloalkyl or phenyl. The reaction is preferably carried out in one of the abovementioned inert diluents with the addition of a suitable base, ie. a base which effects deprotonation of the intermediate VI, at from room temperature to the boiling point of the solvent.

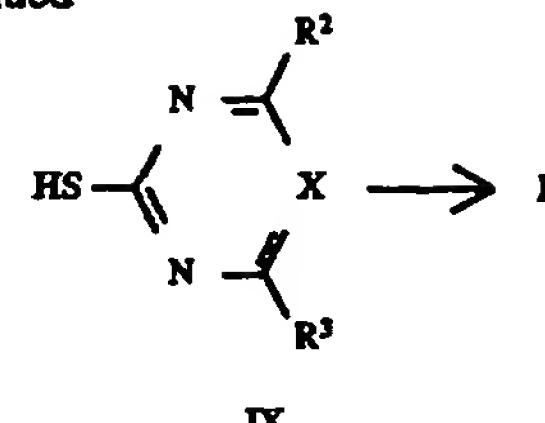
The bases may be an alkali metal or alkaline earth metal hydride, such as sodium hydride, potassium hydride or calcium hydride, a carbonate, such as an alkali metal carbonate, for example, sodium carbonate or potassium carbonate, an alkali metal or alkaline earth metal hydroxide, such as sodium hydroxide or potassium hydroxide, an organometallic compound, such as butyllithium, or an alkali metal amide, such as lithium diisopropylamide.

The novel compounds in which Y is sulfur and the remaining substituents have the meanings stated under the general formula I can be prepared, for example, by reacting 3-(het)arylcarboxylic acid derivatives of the general formula VIII, which are obtainable in a known manner from compounds of the general formula VI and in which the substituents have the abovementioned meanings, with compounds of the general formula IX where R^2 , R^3 and X have the meanings stated under the general formula I.



VIII

-continued



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The reaction is preferably carried out in one of the abovementioned inert diluents with the addition of a suitable base, ie. a base which effects deprotonation of the intermediate IX, at from room temperature to the boiling point of the solvent.

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The bases used may be organic bases, such as tertiary amines, for example triethylamine, pyridine, imidazole or diazabicyclo-undecene, in addition to the abovementioned bases.

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Compounds of the formula I can also be prepared by starting from the corresponding carboxylic acids, ie. compounds of the formula I in which R^1 is hydroxyl, and first converting these in a conventional manner into an activated form, such as a halide, an anhydride or an imidazolide, and then reacting this with a corresponding hydroxyl compound HOR^{10} . This reaction can be carried out in the conventional solvents and often requires the addition of a base, the abovementioned bases being suitable. These two steps can 25 also be simplified, for example, by allowing the carboxylic acid to act on the hydroxy compound in the presence of a water-eliminating agent, such as a carbodiimide.

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In addition, compounds of the formula I can also be prepared by starting from the salts of the corresponding carboxylic acids, ie. from compounds of the formula I in which R is COR^1 and R^1 is OM , where M may be an alkali metal cation or one equivalent of an alkaline earth metal cation. These salts can be reacted with many compounds of the formula R^1-A , where A is a conventional nucleofugic 35 leaving group, for example halogen, such as chlorine, bromine or iodine, or aryl- or alkylsulfonyl which is unsubstituted or substituted by halogen, alkyl or haloalkyl, eg. toluenesulfonyl and methylsulfonyl, or another equivalent leaving group. Compounds of the formula R^1-A having a 40 reactive substituent A are known or can be readily obtained on the basis of general technical knowledge. The reaction 45 can be carried out in the conventional solvents and is effected advantageously with the addition of a base, the abovementioned bases being suitable.

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R in the formula I can be widely varied. For example, R is a group



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where R^1 has the following meanings:

- a) hydrogen,
- b) a succinylimidoxy group;
- c) a 5-membered heteroaromatic structure which is bonded via a nitrogen atom, such as pyrrolyl, pyrazolyl, imidazolyl or triazolyl, and which may carry one or two halogen atoms, in particular fluorine or chlorine and/or one or two of the following radicals:
- 60 C_1-C_4 -alkyl, such as methyl, ethyl, 1-propyl, 2-propyl, 2-methyl-2-propyl, 2-methyl-1-propyl, 1-butyl or 2-butyl;

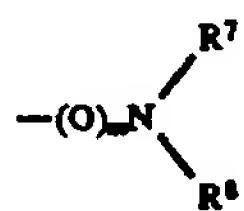
C_1 - C_4 -haloalkyl, in particular C_1 - or C_2 -haloalkyl, for example fluoromethyl, difluoromethyl, trifluoromethyl, chlorodifluoromethyl, dichlorodifluoromethyl, trichloromethyl, 1-fluoroethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2-chloro-2,2-difluoroethyl, 2,2-dichloro-2-fluoroethyl, 2,2,2-trifluoroethyl or pentafluoroethyl;

C_1 - C_4 -haloalkoxy, in particular C_1 - or C_2 -haloalkoxy, such as difluoromethoxy, trifluoromethoxy, chlorodifluoromethoxy, 1-fluoroethoxy, 2-fluoroethoxy, 2,2-difluoroethoxy, 1,1,2,2-tetrafluoroethoxy, 2,2,2-trifluoroethoxy, 2-chloro-1,1,2-trifluoroethoxy or pentafluoroethoxy, in particular trifluoromethoxy;

C_1 - C_4 -alkoxy, such as methoxy, ethoxy, propoxy, 1-methylethoxy, butoxy, 1-methylpropoxy, 2-methylpropoxy or 1,1-dimethylethoxy, in particular methoxy, ethoxy or 1-methylethoxy;

C_1 - C_4 -alkylthio, such as methylthio, ethylthio, propylthio, 1-methylethylthio, butylthio, 1-methylpropylthio, 2-methyl-propylthio or 1,1-dimethylethylthio, in particular methylthio or ethylthio;

d) R^1 is furthermore a radical



where m is 0 or 1 and R⁷ and R⁸ may be identical or different and have the following meanings:
hydrogen;

C_1 - C_8 -alkyl, in particular C_1 - C_4 -alkyl as tested above;

C_3 - C_6 -alkenyl, such as 2-propenyl, 2-butenyl, 3-butenyl, 1-methyl-2-propenyl, 2-methyl-2-propenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-methyl-2-butenyl, 2-methyl-3-butenyl, 3-methyl-2-butenyl, 1-methyl-3-butenyl, 2-methyl-3-butenyl, 3-methyl-3-butenyl, 1,1-dimethyl-2-propenyl, 1,2-dimethyl-2-propenyl, 1-ethyl-2-propenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 1-methyl-2-pentenyl, 2-methyl-2-pentenyl, 3-methyl-2-pentenyl, 4-methyl-2-pentenyl, 3-methyl-3-pentenyl, 4-methyl-3-pentenyl, 1-methyl-4-pentenyl, 2-methyl-4-pentenyl, 3-methyl-4-pentenyl, 4-methyl-4-pentenyl, 1,1-dimethyl-2-butenyl, 1,1-dimethyl-3-butenyl, 1,2-dimethyl-2-butenyl, 1,2-dimethyl-3-butenyl, 1,3-dimethyl-2-butenyl, 1,3-dimethyl-3-butenyl, 2,2-dimethyl-3-butenyl, 2,3-dimethyl-2-butenyl, 2,3-dimethyl-3-butenyl, 1-ethyl-2-butenyl, 1-ethyl-3-butenyl, 2-ethyl-2-butenyl, 2-ethyl-3-butenyl, 1,1,2-trimethyl-2-propenyl, 1-ethyl-1-methyl-2-propenyl or 1-ethyl-2-methyl-2-propenyl, in particular 2-propenyl, 2-butene, 3-methyl-2-butenyl or 3-methyl-2-pentenyl;

C_3 - C_6 -alkynyl such as 2-propynyl, 2-butynyl, 3-butynyl, 1-methyl-2-propynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-methyl-3-butynyl, 2-methyl-3-butynyl, 1-methyl-2-butynyl, 1,1-dimethyl-2-propynyl, 1-ethyl-2-propynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-methyl-2-pentynyl, 1-methyl-2-pentynyl, 1-methyl-3-pentynyl, 1-methyl-4-pentynyl, 2-methyl-3-pentynyl, 2-methyl-4-pentynyl, 3-methyl-4-pentynyl, 4-methyl-2-pentynyl, 1,1-dimethyl-2-butynyl, 1,1-dimethyl-3-butynyl, 1,2-dimethyl-3-butynyl, 2,2-dimethyl-3-butynyl, 1-ethyl-2-butynyl, 1-ethyl-3-butynyl, 2-ethyl-3-butynyl or 1-ethyl-1-butynyl;

methyl-2-propynyl, preferably 2-propynyl, 2-butynyl, 1-methyl-2-propynyl or 1-methyl-2-butynyl, in particular 2-propynyl;

C_3 - C_8 -cycloalkyl, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, cyclooctyl, where these alkyl, cycloalkyl, alkenyl and alkynyl groups may each carry one to five halogen atoms, in particular fluorine or chlorine, and/or one or two of the following groups:

C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy, C_1 - C_4 -alkylthio, C_1 - C_4 -haloalkoxy as stated above, C_3 - C_6 -alkenyloxy, C_3 - C_6 -alkenylthio, C_3 - C_6 -alkynylthio, where the alkenyl and alkynyl moieties present in these radicals preferably have the abovementioned meanings;

C_1 - C_4 -alkylcarbonyl, in particular methylcarbonyl, ethylcarbonyl, propylcarbonyl, 1-methylethylcarbonyl, butylcarbonyl, 1-methylpropylcarbonyl, 2-methylpropylcarbonyl, 1,1-dimethylethylcarbonyl;

C_1 - C_4 -alkoxycarbonyl, such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, 1-methylethoxycarbonyl, butoxycarbonyl, 1-methylpropoxycarbonyl, 2-methylpropoxycarbonyl, 1,1-dimethylethoxycarbonyl;

C_3 - C_6 -alkenylcarbonyl, C_3 - C_6 -alkynylcarbonyl, C_3 - C_6 -alkenyloxycarbonyl or C_3 - C_6 -alkynyloxycarbonyl, where the alkenyl and alkynyl radicals are preferably defined as stated individually above;

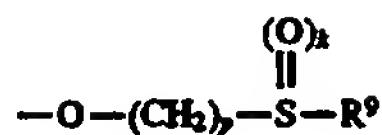
phenyl, unsubstituted or monosubstituted or polysubstituted, for example monosubstituted to trisubstituted, by halogen, nitro, cyano, C_1 - C_4 -alkyl, C_1 - C_4 -haloalkyl, C_1 - C_4 -alkoxy, C_1 - C_4 -haloalkoxy or C_1 - C_4 -alkylthio, for example 2-fluorophenyl, 3-chlorophenyl, 4-bromophenyl, 2-methylphenyl, 3-nitrophenyl, 4-cyanophenyl, 2-trifluoromethylphenyl, 3-methoxyphenyl, 4-trifluoroethoxyphenyl, 2-methylthiophenyl, 2,4-dichlorophenyl, 2-methoxy-3-methylphenyl, 2,4-dimethoxyphenyl, 2-nitro-5-cyanophenyl or 2,6-difluorophenyl;

di- C_1 - C_4 -alkylamino, in particular dimethylamino, dipropylamino, N-propyl-N-methylamino, N-propyl-N-ethylamino, diisopropylamino, N-isopropyl-N-methylamino, N-isopropyl-N-ethylamino or N-isopropyl-N-propylamino;

R^7 and R^8 are each furthermore phenyl, which may be substituted by one or more, for example one to three, of the following radicals: halogen, nitro, cyano, C_1 - C_4 -alkyl, C_1 - C_4 -haloalkyl, C_1 - C_4 -alkoxy, C_1 - C_4 -haloalkoxy or C_1 - C_4 -alkylthio, as stated in particular above;

or R^7 and R^8 together form a cyclic, optionally substituted, for example C_1 - C_4 -alkyl-substituted, C_4 - C_7 -alkylene chain which may contain a heteroatom selected from the group consisting of oxygen, sulfur and nitrogen, such as $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-(CH_2)_7-$, $-(CH_2)_2-O-(CH_2)_2-$, $-CH_2-S-(CH_2)_3-$, $-(CH_2)_2-O-(CH_2)_3-$, $-NH-(CH_2)_3-$, $-CH_2-NH-(CH_2)_2-$, $-CH_2-CH=CH-CH_2-$ or $-CH=CH-(CH_2)_3-$;

c) R^1 is furthermore a group



where k is 0, 1 or 2, p is 1, 2, 3 or 4 and R^9 is C_1-C_4 -alkyl, C_1-C_4 -haloalkyl, C_3-C_6 -alkenyl, C_3-C_6 -alkynyl or unsubstituted or substituted phenyl, as stated in particular above.

f) R^1 is furthermore a radical OR^{10} , where R^{10} is:

hydrogen, the cation of an alkali metal, such as lithium, sodium or potassium, or the cation of an alkaline earth metal, such as calcium, magnesium or barium, or an environmentally compatible organic ammonium ion, such as tertiary C_1-C_4 -alkylammonium or the ammonium ion;

C_3-C_6 -cycloalkyl as stated above, which may carry one to three C_1-C_4 -alkyl groups;

C_1-C_8 -alkyl, in particular methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,2-dimethylpropyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethylbutyl, 2-ethylbutyl, 1-ethyl-2-methylpropyl, which may carry one to five halogen atoms, in particular fluorine or chlorine, and/or one of the following radicals:

C_1-C_4 -alkoxy, C_1-C_4 -alkylthio, cyano, C_1-C_4 -alkylcarbonyl, C_3-C_8 -cycloalkyl [sic], C_1-C_4 -alkoxycarbonyl, phenyl, phenoxy or phenylcarbonyl, where the aromatic radicals in turn may each carry one to five halogen atoms and/or one to three of the following radicals: nitro, cyano, C_1-C_4 -alkyl, C_1-C_4 -haloalkyl, C_1-C_4 -alkoxy, C_1-C_4 -haloalkoxy and/or C_1-C_4 -alkylthio, as stated in particular above;

C_1-C_8 -alkyl as stated above, which may carry one to five halogen atoms, in particular fluorine and/or chlorine, and carries one of the following radicals: a 5-membered heteroaromatic structure which contains one to three nitrogen atoms, or a 5-membered heteroaromatic structure which contains one nitrogen atom and one oxygen or sulfur atom and which may carry one to four halogen atoms and/or one or two of the following radicals:

nitro, cyano, C_1-C_4 -alkyl, C_1-C_4 -haloalkyl, C_1-C_4 -alkoxy, phenyl, C_1-C_4 -haloalkoxy and/or C_1-C_4 -alkylthio. Particular examples are: 1-pyrazolyl, 3-methyl-1-pyrazolyl, 4-methyl-1-pyrazolyl, 3,5-dimethyl-1-pyrazolyl, 3-phenyl-1-pyrazolyl, 4-phenyl-1-pyrazolyl, 4-chloro-1-pyrazolyl, 4-bromo-1-pyrazolyl, 1-imidazolyl, 1-benzimidazolyl, 1,2,4-triazol-1-yl, 3-methyl-1,2,4-triazol-1-yl, 5-methyl-1,2,4-triazol-1-yl, 1-benzotriazolyl, 3-isopropylisoxazol-5-yl, 3-methylisoxazol-5-yl, oxazol-2-yl, thiazol-2-yl, imidazol-2-yl, 3-ethylisoxazol-5-yl, 3-phenylisoxazol-5-yl, 3-tert-butylisoxazol-5-yl;

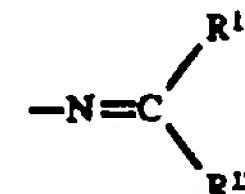
C_2-C_6 -alkyl which carries one of the following radicals in the 2 position: C_1-C_4 -alkoxyimino, C_3-C_6 -alkynyoxyimino, C_3-C_6 -haloalkenyoxyimino or benzoyoxyimino;

C_3-C_6 -alkenyl or C_3-C_6 -alkynyl, where these groups in turn may carry one to five halogen atoms;

R^{10} is furthermore phenyl which may carry one to five halogen atoms and/or one to three of the following radicals: nitro, cyano, C_1-C_4 -alkyl, C_1-C_4 -haloalkyl, C_1-C_4 -alkoxy, C_1-C_4 -haloalkoxy and/or C_1-C_4 -alkylthio, as stated in particular above;

a 5-membered heteroaromatic structure which is bonded via a nitrogen atom, contains one to three nitrogen atoms and may carry one or two hydrogen atoms and/or one or two of the following radicals: C_1-C_4 -alkyl, C_1-C_4 -haloalkyl, C_1-C_4 -alkoxy, phenyl, C_1-C_4 -haloalkoxy and/or C_1-C_4 -alkylthio. Particular examples are 1-pyrazolyl, 3-methyl-1-pyrazolyl, 4-methyl-1-pyrazolyl, 3,5-dimethyl-1-pyrazolyl, 3-phenyl-1-pyrazolyl, 4-phenyl-1-pyrazolyl, 4-chloro-1-pyrazolyl, 4-bromo-1-pyrazolyl, 1-imidazolyl, 1-benzimidazolyl, 1,2,4-triazol-1-yl, 3-methyl-1,2,4-triazol-1-yl, 5-methyl-1,2,4-triazol-1-yl, 1-benzotriazolyl and 3,4-dichloroimidazol-1-yl;

R^{10} is furthermore a group



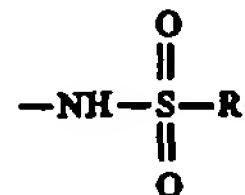
where R^{11} and R^{12} may be identical or different and are each:

C_1-C_8 -alkyl, C_3-C_6 -alkenyl, C_3-C_6 -alkynyl or C_3-C_6 -cycloalkyl, where these radicals may carry C_1-C_4 -alkoxy, C_1-C_4 -alkylthio and/or unsubstituted or substituted phenyl, as stated in particular above;

phenyl, which may be substituted by one or more, for example one to three, of the following radicals: halogen, nitro, cyano, C_1-C_4 -alkyl, C_1-C_4 -haloalkyl, C_1-C_4 -alkoxy, C_1-C_4 -haloalkoxy or C_1-C_4 -alkylthio, where these radicals correspond in particular to the abovementioned ones;

or R^{11} and R^{12} together form a C_3-C_{12} -alkylene chain which may carry one to three C_1-C_4 -alkyl groups and may contain a heteroatom selected from the group consisting of oxygen, sulfur and nitrogen, as stated in particular for R^7 and R^8 .

g) R^1 is furthermore a radical



where R^{13} is:

C_1-C_4 -alkyl, C_3-C_6 -alkenyl, C_3-C_6 -alkynyl, C_3-C_6 -cycloalkyl as stated in particular above, where these radicals may carry C_1-C_4 -alkoxy, C_1-C_4 -alkylthio and/or phenyl as stated above;

phenyl, unsubstituted or substituted, in particular as stated above.

With regard to the biological activity, preferred 3-(het) aryl-oxy(thio)carboxylic acid derivatives are those of the general formula I in which the substituents have the following meanings:

R^2 is one of the C_1-C_4 -alkyl, C_1-C_4 -haloalkyl, C_1-C_4 -alkoxy, C_1-C_4 -haloalkoxy or C_1-C_4 -alkylthio groups stated individually in the case of R^1 or is halogen, in particular chlorine, methyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy or particularly preferably methoxy;

X is nitrogen or CR¹⁴, where

R¹⁴ is hydrogen or, together with R³, forms a 4-membered or 5-membered alkylene or alkenylene chain, in each of which a methylene group is replaced by oxygen, such as —CH₂—CH₂—O—, —CH=CH—O—, —CH₂—CH₂—O— or —CH=CH—CH₂O— [sic], in particular hydrogen or —CH₂—CH₂—O—;

R³ is one of the C₁—C₄-alkyl, C₁—C₄-haloalkyl, C₁—C₄-alkoxy, C₁—C₄-haloalkoxy or C₁—C₄-alkylthio groups stated in the case of R¹ or is halogen, in particular chlorine, methyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy or is bonded to R¹⁴ as stated above to form a 5-membered or 6-membered ring, R³ is particularly preferably methoxy;

R⁴ is 5-membered or 6-membered heteroaryl, such as furyl, thienyl, pyrrol, pyrazolyl, imidazolyl, triazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, thiadiazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, for example 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrrolyl, [sic] 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, oxa-2,4-diazolyl, oxa-3,4-diazolyl [sic], thia-2,4-diazolyl, thia-3,4-diazolyl or triazolyl, where the heteroaromatic structures may carry one to five halogen atoms as stated above, in particular fluorine or chlorine and/or one to three of the following radicals:

C₁—C₄-alkyl, C₁—C₄-alkoxy, C₁—C₄-alkylthio, cyano, nitro, C₁—C₈-alkylcarbonyl, C₁—C₈-alkoxycarbonyl, phenyl, phenoxy or phenylcarbonyl as stated in general and in particular above;

R⁴ is furthermore phenyl or naphthyl, each of which may be substituted by one or more, eg. one to three, of the

following radicals: halogen, nitro, cyano, hydroxyl, mercapto, amino, C₁—C₄-alkyl, C₁—C₄-haloalkyl, C₁—C₄-alkoxy, C₁—C₄-haloalkoxy, C₁—C₄-alkylthio, C₁—C₄-alkylamino or di-C₁—C₄-alkylamino, C₁—C₄-alkylcarbonyl, C₁—C₄-alkoxycarbonyl, in particular as stated in the case of R⁷ and R⁸ or for example 3-hydroxyphenyl, 4-dimethylaminophenyl, 2-mercaptophenyl, 3-methoxycarbonylphenyl, 4-acetylphenyl, 1-naphthyl, 2-naphthyl, 3-bromo-2-naphthyl, 4-methyl-1-naphthyl, 5-methoxy-1-naphthyl, 6-trifluoromethyl-1-naphthyl [sic], 7-chloro-1-naphthyl or 8-hydroxy-1-naphthyl;

R⁵ is hydrogen, C₁—C₄-alkyl, C₃—C₆-alkenyl, C₃—C₆-alkynyl, C₃—C₇-cycloalkyl, C₁—C₄-haloalkyl, C₁—C₄-alkoxyalkyl, C₁—C₄-alkylthioalkyl or phenyl as stated above in particular for R₄;

R⁶ is C₁—C₈-alkyl, C₂—C₆-alkenyl, C₃—C₆-alkynyl or C₃—C₈-cycloalkyl as stated in particular above, each of which may be mono- to polysubstituted by the following radicals: halogen, nitro, cyano, C₁—C₄-alkoxy, C₃—C₆-alkenyl, C₃—C₆-alkynyl, C₁—C₄-alkylthio, C₁—C₄-haloalkoxy, C₁—C₄-alkylcarbonyl, C₁—C₄-alkoxycarbonyl, C₁—C₄-alkylamino or di-C₁—C₄-alkylamino or unsubstituted or substituted phenyl or phenoxy, as stated in particular above;

Y is sulfur, oxygen or a single bond and

Z is sulfur or oxygen,

with the proviso that R⁶ is not unsubstituted C₁—C₄-alkyl when R⁴ is unsubstituted phenyl, Z is oxygen and simultaneously R⁵ is methyl or hydrogen.

Compounds of the formula I where R² and R³ are each methoxy and X is CH are particularly preferred. Examples of preferred compounds are listed in the following table. The definitions given for R⁴ there and in Tables 1 and 2 are likewise to be regarded as preferred, irrespective of the definitions of radicals in combination with R⁴.

TABLE

R ¹	R ⁴	R ⁵	R ⁶	R ²	R ³	X	Y	Z
OH	Phenyl	Methyl	Methyl	OCH ₃	OCH ₃	CH	S	S
OH	Phenyl	Methyl	Methyl	OCH ₃	OCH ₃	CH	O	S
OCH ₃	Phenyl	Methyl	Methyl	OCH ₃	OCH ₃	CH	S	S
OH	Phenyl	i-Propyl	Methyl	OCH ₃	OCH ₃	CH	O	O
OCH ₃	2-Fluorophenyl	Ethyl	Methyl	OCH ₃	OCH ₃	CH	O	O
OC ₂ H ₅	3-Chlorophenyl	Propyl	Methyl	OCH ₃	OCH ₃	N	O	O
ON(CH ₃) ₂	4-Bromophenyl	i-Propyl	Methyl	CF ₃	CF ₃	CH	S	O
ON=C(CH ₃) ₂	2-Thienyl	Methyl	Methyl	OCF ₃	OCF ₃	CH	O	S
HNSO ₂ C ₆ H ₅	3-Thienyl	Methyl	Methyl	CH ₃	CH ₃	CH	O	O
NHPhenyl	2-Puryl	Methyl	Methyl	Cl	Cl	CH	O	O
ONa	3-Puryl	Methyl	Methyl	OCH ₃	—OCH ₂ —CH ₂ —		S	O
O—CH ₂ —C≡CH	Phenyl	Ethyl	OCH ₃	CF ₃	CH	O	O	
OH	Phenyl	Propyl	Propyl	OCH ₃	OCH ₃	CH	O	S
OCH ₃	Phenyl	i-Propyl	i-Propyl	OCH ₃	CH ₃	CH	O	O
OC ₂ H ₅	Phenyl	Methyl	s-Butyl	OCH ₃	Cl	CH	S	O
ON(CH ₃) ₂	2-Methylphenyl	Methyl	Methyl	OCH ₃	OCH ₃	CH	O	O
ON(CH ₃) ₂	3-Methoxyphenyl	Methyl	Methyl	OCH ₃	OCH ₃	CH	O	O
ON=C(CH ₃) ₂	4-Nitrophenyl	Methyl	Methyl	OCH ₃	OCH ₃	CH	O	O
NHPhenyl	2-Oxazolyl	Methyl	Methyl	CF ₃	CF ₃	N	S	O
ONa	4-Oxazolyl	Methyl	Propen-3-yl	OCF ₃	OCF ₃	N	O	S
O—CH ₂ —C≡CH	5-Oxazolyl	Methyl	Propyn-3-yl	CH ₃	CH ₃	N	O	O
OH	3-Isoxazolyl	Methyl	Cyclopentyl	Cl	Cl	N	O	O
OCH ₃	4-Isoxazolyl	Methyl	Cyclohexyl	OCH ₃	—OCH ₂ —CH ₂ —		O	O
OC ₂ H ₅	5-Isoxazolyl	Methyl	Cyclopropylmethyl	OCH ₃	CF ₃	N	S	O
ON(CH ₃) ₂	Phenyl	Methyl	1-Phenylpropyl-3-yl	OCH ₃	OCF ₃	N	O	S
ON=C(CH ₃) ₂	2-Hydroxyphenyl	Methyl	Methyl	OCH ₃	CH ₃	N	O	O
ONSO ₂ C ₆ H ₅	3-Trifluoromethylphenyl	Methyl	Methyl	OCH ₃	Cl	N	O	O

TABLE-continued

R ¹	R ⁴	R ⁵	R ⁶	R ²	R ³	X	Y	Z
NHPhenyl	4-Dimethylaminophenyl	Methyl	Methyl	OCH ₃	OCH ₃	CH	S	O
ONa	2-Imidazolyl	Ethyl	Methyl	OCH ₃	OCH ₃	CH	S	S
O—CH ₂ —C≡CH	4-Imidazolyl	Propyl	Methyl	OCH ₃	OCH ₃	N	S	S
OH	3-Pyrazolyl	i-Propyl	Methyl	CF ₃	CF ₃	CH	O	S
OCH ₃	4-Pyrazolyl	Methyl	Methyl	OCP ₃	OCP ₃	CH	O	O
OC ₂ H ₅	Phenyl	Methyl	Trifluoroethyl	CH ₃	CH ₃	CH	O	O
ON(CH ₃) ₂	Phenyl	Methyl	Benzyl	Cl	Cl	CH	O	O
ON(CH ₃) ₂	Phenyl	Methyl	2-Methoxyethyl	OCH ₃	—OCH ₂ —CH ₂ —	S	O	O
ON=C(CH ₃) ₂	Phenyl	Methyl	3-Methoxycarbonylpropyl	OCH ₃	CF ₃	N	S	S
NH-Phenyl	2-Pyridyl	Methyl	2-Chloroethyl	OCH ₃	OCP ₃	N	S	S
ONa	3-Pyridyl	Methyl	Methyl	OCH ₃	CH ₃	N	O	O
O—CH ₂ —C≡CH	4-Pyridyl	Methyl	Methyl	OCH ₃	Cl	N	O	O

The compounds I and the herbicides containing them and their environmentally compatible salts of alkali metals and alkaline earth metals ensure very good control of weeds and grass weeds in crops such as wheat, rice and corn, soybean and cotton, without damaging the crops, an effect which occurs in particular at low application rates.

They may be applied, for example, in the form of directly sprayable solutions, powders, suspensions, including concentrated aqueous, oily or other suspensions or dispersions, emulsions, oil dispersions, pastes, dusting agents, broadcasting agents or granules, by spraying, nebulizing, dusting, broadcasting or pouring. The application forms depend on the intended uses; they should in any case ensure a very fine distribution of the novel active ingredients.

The compounds I are suitable in general for the preparation of directly sprayable solutions, emulsions, pastes or oil dispersions. Suitable inert additives include mineral oil fractions having a medium to high boiling point, such as kerosine or diesel oil, and coal tar oils and oils of vegetable or animal origin, aliphatic, cyclic and aromatic hydrocarbons, e.g. toluene, xylene, paraffin, tetrahydronaphthalene, alkylated naphthalenes or derivatives thereof, methanol, ethanol, propanol, butanol, cyclohexanol, cyclohexanone, chlorobenzene, isophorone or strongly polar solvents, such as N,N-dimethylformamide, dimethyl sulfoxide, N-methylpyrrolidone or water.

Aqueous application forms can be prepared from emulsion concentrates, dispersions, pastes, wettable powders or water-dispersable granules by adding water. For the preparation of emulsions, pastes or oil dispersions, the substrates [sic] as such are dissolved in an oil or solvent, can be homogenized in water by means of wetting agents, adherents, dispersants or emulsifiers. However, it is also possible to prepare concentrates which consist of active ingredient, wetting agents, adherents, dispersants or emulsifiers and possibly solvents or oil and which are suitable for dilution with water.

Suitable surfactants are alkali metal, alkaline earth metal and ammonium salts of aromatic sulfonic acids, for example ligninsulfonic, phenolsulfonic, naphthalenesulfonic and dibutylnaphthalenesulfonic acid, and of fatty acids, alkanesulfonates, alkylarylsulfonates, alkylsulfates, lauryl ether sulfates and fatty alcohol sulfates, and salts of sulfated hexa-, hepta- and octadecanols and of fatty alcohol glycol ethers, condensates of sulfonated naphthalene and its derivatives with formaldehyde, condensates of naphthalene or of naphthalene sulfonic acids with phenol and formaldehyde, polyoxyethylene octylphenyl ether, ethoxylated isoctyl-, octyl- or nonylphenyl, alkylphenyl polyglycol ether, tributylphenyl polyglycol ether, alkylaryl polyether alcohols,

isotridecyl alcohol, fatty alcohol/ethylene oxide condensates, ethoxylated castor oil, polyoxyethylene alkyl ether or polyoxypropylene [lacuna], lauryl alcohol polyglycol ether acetate, sorbitol esters, lignin sulfite waste liquors or methyl cellulose.

Powders, broadcasting agents and dusting agents can be prepared by mixing or milling the active ingredients together with a solid carrier.

Granules, for example coated, impregnated and homogeneous granules, can be prepared by binding the active ingredients to solid carriers. Solid carriers are mineral earths such as silicas, silica gels, silicates, talc, kaolin, limestone, lime, chalk, btle, loess, clay, dolomite, kieselguhr, calcium sulfate, magnesium sulfate, magnesium oxide, milled plastics, fertilizers, such as ammonium sulfate, ammonium phosphate, ammonium nitrate and ureas, and vegetable products, such as grain flour, bark meal, wood meal and nutshell meal, cellulosic powders and other solid carriers.

The formulations contain in general from 0.01 to 95, preferably from 0.5 to 90%, by weight of active ingredient. The active ingredients are used in the purity of from 90 to 100%, preferably from 95 to 100% (according to the NMR spectrum).

Examples of formulations are:

- I. 20 parts by weight of compound No. 2.1 are dissolved in a mixture which consists of 80 parts by weight of alkylated benzene, 10 parts by weight of the adduct of from 8 to 10 mol of ethylene oxide with 1 mol of N-monoethanolamide, 5 parts by weight of the calcium salt of dodecylbenzenesulfonic acid and 5 parts by weight of the adduct of 40 mol of ethylene oxide with 1 mol of castor oil. By pouring the solution into 100,000 parts by weight of water and finely distributing it therein, an aqueous dispersion which contains 0.02% by weight of the active ingredient is obtained.
- II. 20 parts by weight of compound No. 2.1 are dissolved in a mixture which consists of 40 parts by weight of cyclohexanone, 30 parts by weight of isobutanol, 20 parts by weight of the adduct of 7 mol of ethylene oxide with 1 mol of isoctylphenol and 10 parts by weight of the adduct of 40 mol of ethylene oxide with 1 mol of castor oil. By pouring the solution into 100,000 parts by weight of water and finely distributing it therein, an aqueous dispersion which contains 0.02% by weight of the active ingredient is obtained.
- III. 20 parts by weight of active ingredient No. 2.1 are dissolved in a mixture which consists of 25 parts by weight of cyclohexanone, 65 parts by weight of a mineral

oil fraction boiling within the range from 210° to 280° C. and 10 parts by weight of the adduct of 40 mol of ethylene oxide with 1 mol of castor oil. By pouring the solution into 100,000 parts by weight of water and finely distributing it therein, an aqueous dispersion which contains 0.02% by weight of the active ingredient is obtained.

IV. 20 parts by weight of active ingredient No. 2.1 are thoroughly mixed with 3 parts by weight of the sodium salt of diisobutylnaphthalene- α -sulfonic acid, 17 parts by weight of the sodium salt of a ligninsulfonic acid obtained from a sulfite waste liquor and 60 parts by weight of silica gel powder, and the mixture is milled in a hammer mill. By finely distributing the mixture into 20,000 parts by weight of water, a spray liquor which contains 0.1% by weight of the active ingredient is obtained.

3 parts by weight of active ingredient No. 2.1 are mixed with 97 parts by weight of finely divided kaolin. A dusting agent which contains 3% by weight of the active ingredient is obtained in this manner.

VI. 20 parts by weight of active ingredient No. 2.1 are thoroughly mixed with 2 parts by weight of the calcium salt of dodecylbenzenesulfonic acid, 8 parts by weight of a fatty alcohol polyglycol ether, 2 parts by weight of the sodium salt of a phenol/urea/formaldehyde condensate and 68 parts by weight of a paraffinic mineral oil. A stable oily dispersion is obtained.

Application can be carried out by the preemergence or postemergence method. If the active ingredients are less well tolerated by certain crops, it is possible to use application methods in which the herbicides are sprayed with the aid of the sprayers so that the leaves of the sensitive crops are as far as possible not affected while the active ingredients reach the leaves of undesirable plants growing underneath or the uncovered soil surface (post-directed, lay-by).

The application rates of active ingredient are from 0.001 to 5, preferably from 0.01 to 2, kg/ha of active ingredient (a.i.), depending on the aim of control, the season, the target plants and the stage of growth.

In view of the versatility of the application methods, the novel compounds or the agents containing them can be used in a further number of crops for eliminating undesirable plants. Examples of suitable crops are the following:

Allium cepa, Ananas comosus, Arachis hypogaea, Asparagus officinalis, Beta vulgaris spp. altissima, Beta vulgaris spp. rapa, Brassica napus var. napus, Brassica napus var. napobrassica, Brassica rapa var. silvestris, Camellia sinensis, Carthamus tinctorius, Cary illinoiensis, Citrus limon, Citrus sinensis, Coffea arabica (Coffea canephora, Coffea liberica), Cucumis sativus, Cynodon dactylon, Daucus carota, Elaeis guineensis, Fragaria vesca, Glycine max, Gossypium hirsutum (Gossypium arboreum, Gossypium herbaceum, Gossypium visifolium), Gossypium hirsutum (Gossypium arboreum, Gossypium, [sic] herbaceum, Gossypium visifolium), Helianthus annuus, Hevea brasiliensis, Hordeum vulgare, Humulus lupulus, Ipomoea batatas, Juglans regia, Lens culinaris, Linum usitatissimum, Lycopersicon lycopersicum, Malus spp., Manihot esculenta, Medicago sativa, Musa spp., Nicotiana tabacum (N. rustica), Olea europaea, Oryza sativa, Phaseolus lunatus, Phaseolus vulgaris, Picea abies, Pinus spp., P. isum [sic] sativum, Prunus avium, Prunus persica, Pyrus communis, Ribes sylvestre, Ricinus communis, Saccharum officinarum, Secale cereale, Solanum tuberosum, Sorghum bicolor (S. vulgare), Theobroma cacao, Trifolium pratense, Triticum aestivum, Triticum durum, Vicia faba, Vitis vinifera, Zea mays.

The compounds of the formula I can influence virtually all development stages of a plant in different ways and are

therefore used as growth regulators. The diversity of action of the plant growth regulators depends in particular

- a) on the plant species and variety,
- b) on the time of application, based on the state of development of the plants and on the season
- c) on the place of application and application method (for example seed dressing, soil treatment, foliar application or trunk injection in the case of trees),
- d) on climatic factors, for example temperature and amount of precipitation, as well as length of day and light intensity,
- e) on the soil characteristics (including fertilizer application),
- f) on the formulation or application form of the active ingredient and finally
- g) on the concentration of active ingredient used.

From the many different potential applications of the plant growth regulators of the formula I in plant cultivation, in agriculture and in horticulture, some are mentioned below.

A. With the compounds which can be used according to the invention, it is possible greatly to inhibit the vegetative growth of the plants, which is evident in particular from a reduction in the growth in length.

Accordingly, the treated plants exhibit stunted growth; moreover, a darker leaf coloration is observed.

A reduced intensity of the growth of grasses and crops susceptible to lodging, such as cereals, corn, sunflowers and soybean, proves advantageous in practice. Shortening and strengthening of the stems reduce or eliminate the danger of lodging of plants under unfavorable weather conditions prior to harvesting.

The use of growth regulators for inhibiting the growth in length and for changing the time of ripening in the case of cotton is also important. This permits completely mechanized harvesting of this important crop.

In the case of fruit trees and other trees, pruning costs can be saved by means of the growth regulators. Moreover, the alternation of fruit trees can be broken by means of growth regulators.

By using growth regulators, it is also possible to increase or inhibit the lateral branching of the plants. This is of interest when, for example in the case of tobacco plants, the formation of side shoots is to be inhibited in favor of foliar growth.

Growth regulators can also be used for considerably increasing the resistance to frost, for example in the case of winter rape. On the one hand, the growth in length and the development of foliage and plant mass which is too luxuriant (and therefore particularly susceptible to frost) are inhibited. On the other hand, after sowing and prior to the onset of the winter frost, the young rape plants are held back in the vegetative stage of development in spite of favorable growth conditions. This also eliminates the danger of frost for plants which tend to exhibit premature cessation of inhibition of blooming and to grow over into the generative phase. In other crops too, for example winter cereals, it is advantageous if, through treatment with the novel compounds in the fall, the stocks are well tillered but do not start the winter with too luxuriant a growth. A greater sensitivity to frost and—owing to the relatively small foliage or plant mass—attack by various diseases (for example fungal disease) can thus be prevented.

B. The growth regulators can be used to achieve high yields of both plant parts and plant ingredients. For example, it is possible to induce the growth of larger amounts of buds,

flowers, leaves, fruits, seed kernels, roots and tubers, to increase the content of sugar in sugarbeets, sugar cane and citrus fruits, to increase the protein content of cereals or soybean or to stimulate rubber trees to produce greater latex flow.

The compounds of the formula I can result in higher yields by intervening in the plant metabolism or by promoting or inhibiting vegetative and/or generative growth.

C. Finally, plant growth regulators can be used both for shortening and lengthening the stages of development and for accelerating or slowing down the ripening of the harvested plant parts before or after harvesting.

For example, facilitating harvesting, which is made possible by concentrated dropping or a reduction in the adhesion to a tree in the case of citrus fruits, olives or other species and varieties of pomes, drupes and indehiscent fruit, is of commercial interest. The same mechanism, i.e. promotion of the formation of abscission tissue between fruit or leaf and stem part of the plant is also essential for readily controllable defoliation of crops such as cotton.

D. The growth regulators can furthermore reduce the water consumption of plants. By using the novel substances, it is possible to reduce the intensity of irrigation and hence to carry out more economical farming because, inter alia, the extent of opening of the stomata is reduced, a thicker epidermis and cuticle are formed, the root penetration of the soil is improved and the microclimate in the plant stock is favorably influenced by more compact growth.

Compounds I are particularly suitable for shortening the stems of crops such as barley, rape and wheat.

The active ingredients of the formula I which are to be used according to the invention can be fed to the crops both via the seed (as seed dressing) and via the soil, i.e. through the roots and—particularly preferably—via the foliage by spraying.

The application rate of active ingredient is not critical, owing to the high tolerance by plants. The optimum application rate varies depending on the aim of control, the season, the target plants and the stages of growth.

In the case of seed treatment, in general from 0.001 to 50, preferably from 0.01 to 10, g of active ingredient per kilogram of seed are required.

For foliage and soil treatment, in general doses of from 0.001 to 10, preferably from 0.01 to 3, in particular from 0.01 to 0.5, kg/ha are to be considered sufficient.

In order to broaden the action spectrum and to achieve synergistic effects, the compounds of the formula I may be mixed with many members of other groups of herbicidal or growth-regulating active ingredients and applied together with them. Suitable components of the mixture are, for example, diazines, 4H-3,1-benzoxazine derivatives, benzothiadiazinones, 2,6-dinitroanilines, N-phenylcarbamates, thiocarbamates, halocarboxylic acids, triazines, amides, ureas, diphenyl ethers, triazinones, uracils, benzofuran derivatives, cyclohexane-1,3-dione derivatives which carry, for example, a carboxyl or carbimino group in the 2 position, quinoline carboxylic acid derivatives, imidazolinones, sulfonamides, sulfonylureas, aryloxy- and heteroaryloxyphenoxy-propionic acids and their salts, esters and amides and others.

It may also be useful to apply the compounds of the formula I, alone or in combination with other herbicides, also as a mixture with further crop protection agents, for

example with pesticides or agents for controlling phytopathogenic fungi or bacteria. The miscibility with mineral salt solutions which are used for eliminating nutrient and trace element deficiencies is also of interest. Nonphytotoxic oils and oil concentrates may also be added.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

SYNTHESIS EXAMPLES

Synthesis of compounds of the general formula VI

Example 1

Methyl 3-methoxy-3-(3-methoxyphenyl)-2-hydroxybutyrate

19.5 g (88 mmol) of methyl 3-(3-methoxyphenyl)-2,3-epoxybutyrate are dissolved in 200 ml of absolute methanol, 20 and 0.1 ml of boron trifluoride etherate is added. Stirring is carried out for 12 hours at room temperature and the solvent is distilled off. The residue is taken up in ethyl acetate and the solution is washed with sodium bicarbonate solution and water and dried over sodium sulfate. After the solvent has 25 been distilled off, 21.1 g of a slightly yellow oil remain.

Yield: 94% (diastereomer mixture 1:1)

Example 2

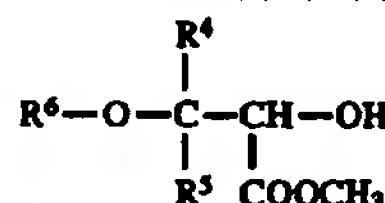
Methyl 3-benzyloxy-3-phenyl-2-hydroxybutyrate

9.6 g (50 mmol) of methyl 3-phenyl-2,3-epoxybutyrate are dissolved in 150 ml of benzyl alcohol, and 0.5 ml of concentrated sulfuric acid is added. Stirring is carried for 6 hours at 50° C. and the mixture is allowed to cool to room temperature. After neutralization with sodium bicarbonate solution, the excess benzyl alcohol is distilled off under greatly reduced pressure 0 and the residue is purified by flash chromatography over silica gel using 9:1 n-hexane/ethyl acetate. After the solvent has been distilled off, 6.5 g of a colorless oil remain.

Yield: 43% (diastereomer mixture 3:2)

All the compounds stated in Table 1 are prepared similarly:

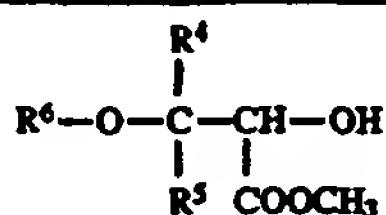
TABLE 1



Intermediates of the formula VI where R^1 is CH_3 .

No.	R^6	R^4	R^5	DR*	Mp. [°C.]
1.1	Methyl	3-Methoxyphenyl	Methyl	1:1	oil
1.2	Benzyl	Phenyl	Methyl	3:2	oil
1.3	Methyl	2-Fluorophenyl	Methyl	1:1	oil
1.4	Methyl	4-i-Propylphenyl	Methyl		
1.5	Methyl	2-Methylphenyl	Methyl	2:1	oil
1.6	Methyl	3-Methylphenyl	Methyl		
1.7	Methyl	4-Methylphenyl	Methyl	3:2	oil
1.8	Methyl	3-Nitrophenyl	Methyl		
1.9	Methyl	4-Bromophenyl	Methyl	3:1	oil
1.10	Methyl	2-Furyl	Methyl		
1.11	Methyl	3-Furyl	Methyl		
1.12	Methyl	2-Thienyl	Methyl		
1.13	Methyl	3-Thienyl	Methyl		
1.14	Methyl	2-Pyridyl	Methyl		

TABLE 1-continued



Intermediates of the formula VI where R^1 is CH_3 .

No.	R^6	R^4	R^5	DR*	Mp. [°C.]
1.15	Methyl	3-Pyridyl	Methyl		
1.16	Methyl	4-Pyridyl	Methyl		
1.17	Methyl	2-Thiazolyl	Methyl		
1.18	Methyl	3-Isoxazolyl	Methyl		
1.19	Methyl	4-Imidazolyl	Methyl		
1.20	Methyl	2-Pyrazolyl	Methyl		
1.21	Methyl	4-Chlorophenyl	Methyl	2:1	oil
1.22	Benzyl	3-Methylphenyl	Methyl	1:1	oil
1.23	Methyl	4-Fluorophenyl	Methyl	1:1	oil
1.24	Benzyl	4-Bromophenyl	Methyl	1:1	oil
1.25	Benzyl	4-Chlorophenyl	Methyl	3:2	oil
1.26	Benzyl	4-Fluorophenyl	Methyl	1:1	oil
1.27	Methyl	Phenyl	Ethyl	1:1	oil
1.28	Methyl	3-Nitrophenyl	Methyl	2:1	oil
1.29	Ethyl	4-Methylphenyl	Methyl	1:1	oil
1.30	Benzyl	4-Methylphenyl	Methyl	1:1	oil
1.31	Benzyl	Phenyl	Ethyl	1:0	oil
1.32	4-Fluorobenzyl	Phenyl	Methyl	1:1	oil

*Diastereomer Ratio

Synthesis of compounds of the general formula I:

Example 3

Methyl 3-benzyloxy-3-phenyl-2-(4,6-dimethoxypyrimidin-2-yloxy)butyrate

3 g (10 mmol) of methyl 3-benzyloxy-3-phenyl-2-hydroxybutyrate (compound 1.1) are dissolved in 40 ml of dimethylformamide, and 0.3 g (12 mmol) of sodium hydride are added. Stirring is carried out for 1 hour, after which 2.2 g (10 mmol) of 4,6-dimethoxy-2-methylsulfonylpyrimidine are added. After stirring has been carried out for 24 hours at room temperature, hydrolysis is effected carefully with 10 ml of water, the pH is brought to 5 with acetic acid and the solvent is distilled off under greatly reduced pressure. The residue is taken up in 100 ml of ethyl acetate, washed with water and dried over sodium sulfate and the solvent is distilled off. 10 ml of methyl tert-butyl ether are added to the residue and the precipitate formed is filtered off with suction. After drying, 2.4 g of a white powder remain.

Yield: 55% (diastereomer mixture 1:1) Mp.: 115°-117° C.

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Example 4

3-Benzyl-3-phenyl-2-(4,6-dimethoxypyrimidin-2-yloxy)butyric acid

1.4 g (3 mmol) of methyl 3-benzyloxy-3-phenyl-2-(4,6-dimethoxypyrimidin-2-yloxy)butyrate (Example 3) are dissolved in 20 ml of methanol and 20 ml of tetrahydrofuran, and 3.7 g of 10% strength NaOH solution are added. Stirring is carried out for 6 hours at 60° C. and for 12 hours at room temperature, the solvent is distilled off under reduced pressure and the residue is taken up in 100 ml of water. Extraction is now carried out with ethyl acetate to remove unconverted ester. The aqueous phase is then brought to pH 1-2 with dilute hydrochloric acid and is extracted with ethyl acetate. After drying has been carried out over magnesium sulfate and the solvent has been distilled off, a little acetone is added to the residue and the precipitate formed is filtered off with suction. After drying, 1.2 g of a white powder remain.

Yield: 88% Mp.: 165° C. (decomposition, diastereomer mixture 3:2)

Example 5

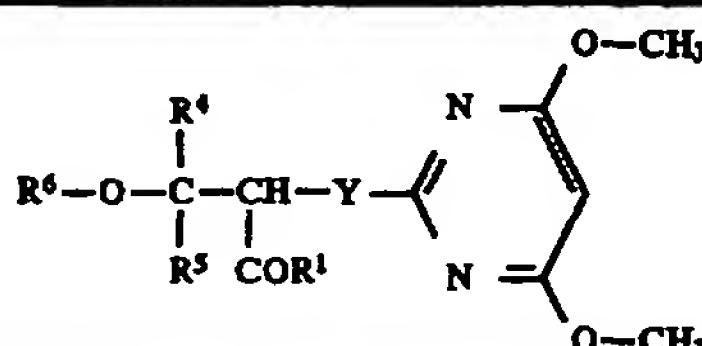
Methyl 3-benzyloxy-3-phenyl-2-(4,6-dimethoxypyrimidin-2-ylthio)butyrate

11 g (25 mmol) of methyl 3-benzyloxy-3-phenyl-2-hydroxybutyrate (compound 1.1) are dissolved in 50 ml of dichloromethane, 3 g (30 mmol) of triethylamine are added and 3.2 g (28 mmol) of methanesulfonyl chloride are added dropwise while stirring. Stirring is continued for 2 hours at room temperature, and the mixture is washed with water, dried over magnesium sulfate and evaporated down under reduced pressure. The residue is taken up in dimethylformamide and the solution is added dropwise at 0° C. to a suspension of 12.9 g (75 mmol) of 4,6-dimethoxypyrimidine-2-thiol and 8.4 g (100 mmol) of sodium bicarbonate in 100 ml of dimethylformamide. After stirring has been carried out for 2 hours at room temperature and for a further 2 hours at 60° C., the mixture is poured onto 11 of ice water and the resulting precipitate is filtered off with suction. After drying, 3.2 g of a white powder remain.

Yield: 29% (diastereomer mixture 1:1)

The compounds stated in Table 2 were prepared similarly to the above examples.

TABLE 2

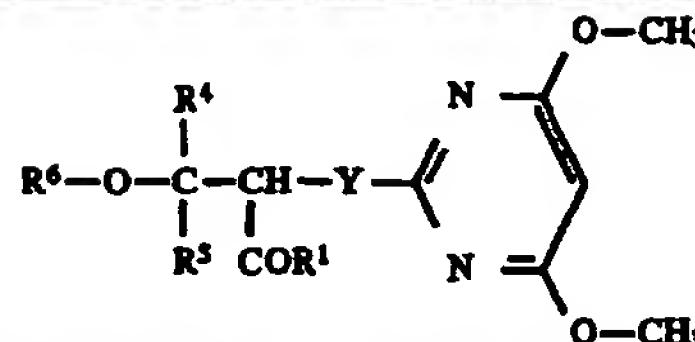


No.	R^6	R^4	R^5	Y	R^1	Diastereomers	Mp. (°C.)
2.1	Benzyl	Phenyl	Methyl	O	OCH_3	1:1	115-117
2.2	Benzyl	Phenyl	Methyl	O	OH	3:2	165 (decomp.)
2.3	Benzyl	Phenyl	Methyl	S	OCH_3	1:1	
2.4	Benzyl	Phenyl	Methyl	S	OH		
2.5	Methyl	2-Fluorophenyl	Methyl	O	OCH_3	1:1	126-128
2.6	Methyl	2-Fluorophenyl	Methyl	O	OH	2:1	185-186

TABLE 2-continued

No.	R ⁶	R ⁴	R ⁵	Y	R ¹	Diastereomers	Mp. (°C.)	
							O	OCH ₃
2.7	Methyl	3-Methoxyphenyl	Methyl	O	OCH ₃	1:0 (5:1)	131-132 (93-95)	
2.8	Methyl	3-Methoxyphenyl	Methyl	O	OH	1:0	187-189	
2.9	Methyl	4-i-Propylphenyl	Methyl	O	OCH ₃			
2.10	Methyl	4-i-Propylphenyl	Methyl	O	OH			
2.11	Methyl	2-Methylphenyl	Methyl	O	OCH ₃	3:1	122-124	
2.12	Methyl	2-Methylphenyl	Methyl	O	OH	1:1	135-137	
2.13	Methyl	3-Methylphenyl	Methyl	O	OCH ₃	1:1	105-110	
2.14	Methyl	3-Methylphenyl	Methyl	O	OH	1:1	130-132	
2.15	Methyl	4-Methylphenyl	Methyl	O	OCH ₃	1:1	99-102	
2.16	Methyl	4-Methylphenyl	Methyl	O	OH	1:1	145-147	
2.17	Methyl	4-Bromophenyl	Methyl	O	OCH ₃	1:0	148-150	
2.18	Methyl	4-Bromophenyl	Methyl	O	OH	1:0	189-190	
2.19	Methyl	2-Furyl	Methyl	O	OCH ₃			
2.20	Methyl	2-Furyl	Methyl	O	OH			
2.21	Methyl	3-Furyl	Methyl	O	OCH ₃			
2.22	Methyl	3-Furyl	Methyl	O	OH			
2.23	Methyl	2-Thienyl	Methyl	O	OCH ₃			
2.24	Methyl	2-Thienyl	Methyl	O	OH			
2.25	Methyl	2-Pyridyl	Methyl	O	OCH ₃	2:1	oil	
2.26	Methyl	2-Pyridyl	Methyl	O	ONa		175-176	
2.27	Methyl	3-Pyridyl	Methyl	O	OCH ₃			
2.28	Methyl	3-Pyridyl	Methyl	O	OH			
2.29	Methyl	4-Pyridyl	Methyl	O	OCH ₃			
2.30	Methyl	4-Pyridyl	Methyl	O	OH			
2.31	Methyl	3-Chlorophenyl	Methyl	O	OCH ₃			
2.32	Methyl	3-Chlorophenyl	Methyl	O	OH			
2.33	Methyl	2-Thiazolyl	Methyl	O	OCH ₃			
2.34	Methyl	2-Thiazolyl	Methyl	O	OH			
2.35	Methyl	3-Isoxazolyl	Methyl	O	OCH ₃			
2.36	Methyl	3-Isoxazolyl	Methyl	O	OH			
2.37	Methyl	4-Imidazolyl	Methyl	O	OCH ₃			
2.38	Methyl	4-Imidazolyl	Methyl	O	OH			
2.39	Methyl	2-Pyrazolyl	Methyl	O	OCH ₃			
2.40	Methyl	2-Pyrazolyl	Methyl	O	OH			
2.41	Benzyl	4-Chlorophenyl	Methyl	O	OCH ₃	1:1	112-114	
2.42	Benzyl	4-Chlorophenyl	Methyl	O	OH			
2.43	i-Propyl	2-Fluorophenyl	Methyl	O	OCH ₃	4:1	115-120	
2.44	i-Propyl	2-Fluorophenyl	Methyl	O	OH	2:1	143-145	
2.45	Methyl	4-Fluorophenyl	Methyl	O	OCH ₃	1:1	122-125	
2.46	Methyl	4-Fluorophenyl	Methyl	O	OH	3:1	170-172	
2.47	Benzyl	3-Methylphenyl	Methyl	O	OCH ₃	1:1	94-95	
2.48	Benzyl	3-Methylphenyl	Methyl	O	OH	1:1	154-156	
2.49	Methyl	4-Chlorophenyl	Methyl	O	OCH ₃	1:1	125-127	
2.50	Methyl	4-Chlorophenyl	Methyl	O	OH	5:1	206-207	
2.51	Methyl	Phenyl	Ethyl	O	OCH ₃	1:0	95-100	
2.52	Methyl	Phenyl	Ethyl	O	OH	1:0	140-142	
2.53	Benzyl	4-Fluorophenyl	Methyl	O	OCH ₃	1:1	95-98	
2.54	Benzyl	4-Fluorophenyl	Methyl	O	OH	4:1	153-154	
2.55	4-Fluorobenzyl	Phenyl	Methyl	O	OCH ₃	1:0	152-153	
2.56	4-Fluorobenzyl	Phenyl	Methyl	O	OH	7:3	160-162	
2.57	4-Bromobenzyl	Phenyl	Methyl	O	OCH ₃	9:1	158-160	
2.58	4-Bromobenzyl	Phenyl	Methyl	O	OH	1:0	203-204	
2.59	Benzyl	2-Fluorophenyl	Methyl	O	OCH ₃	1:0	129-130	
2.60	Benzyl	2-Fluorophenyl	Methyl	O	OH	1:0	200-201	
2.61	Benzyl	4-Bromophenyl	Methyl	O	OCH ₃	1:1	78-79	
2.62	Benzyl	4-Bromophenyl	Methyl	O	OH	1:1	156-158	
2.63	Benzyl	4-Methylphenyl	Methyl	O	OCH ₃	1:1	oil	
2.64	Benzyl	4-Methylphenyl	Methyl	O	OH	4:1	158-159	
2.65	Benzyl	Phenyl	Ethyl	O	OCH ₃	1:0	110-112	
2.66	Benzyl	Phenyl	Ethyl	O	OH	1:0	92-93	
2.67	Ethyl	4-Methylphenyl	Methyl	O	OCH ₃	1:0	117-119	
2.68	Ethyl	4-Methylphenyl	Methyl	O	OH	1:1	oil	
2.69	Methyl	2-Furyl	H	O	OCH ₃	1:1	oil	
2.70	Methyl	2-Furyl	H	O	OH	1:1	oil	
2.71	4-Chlorobenzyl	Phenyl	Methyl	O	OCH ₃	1:0	172-174	
2.72	4-Chlorobenzyl	Phenyl	Methyl	O	OH	1:0	60-61	
2.73	2-Butyl	4-Bromophenyl	Methyl	O	OCH ₃	—	104-106	
2.74	2-Butyl	4-Bromophenyl	Methyl	O	OH	1:0	153-154	

TABLE 2-continued



No.	R ⁶	R ⁴	R ³	Y	R ¹	Diastereomers	Mp. (°C.)
2.75	n-Propyl	4-Fluorophenyl	Methyl	O	OCH ₃	9:1	119-120
2.76	n-Propyl	4-Fluorophenyl	Methyl	O	OH	9:1	104-105
2.77	Methyl	3-Nitrophenyl	Methyl	O	OCH ₃	1:1	101-102
2.78	Methyl	3-Nitrophenyl	Methyl	O	OH	1:1	165-172
2.79	Methyl	4-Trifluorophenyl	Methyl	O	OCH ₃	1:0	112-113
2.80	Methyl	4-Trifluorophenyl	Methyl	O	OH	4:1	68-70
2.81	Methyl	3-Thienyl	H	O	OCH ₃	1:1	80-82
2.82	Methyl	3-Thienyl	H	O	OH	1:1	oil
2.83	4-Chlorobenzyl	Phenyl	Methyl	O	OCH ₃	0:1	112-113
2.84	4-Chlorobenzyl	Phenyl	Methyl	O	OCH ₃	0:1	60-61
2.85	Methyl	Phenyl	Ethyl	O	OCH ₃	1:3	125-130
2.86	Methyl	Phenyl	Ethyl	O	OH	0:1	133-135
2.87	Benzyl	3-Methoxyphenyl	Methyl	O	OCH ₃	3:1	86-87
2.88	Benzyl	3-Methoxyphenyl	Methyl	O	OH	1:0	155
2.89	Benzyl	3-Methoxyphenyl	Methyl	O	OH	0:1	138-140
2.90	2-Phenylethyl	Phenyl	Methyl	O	OH	1:0	147-149
2.91	Methyl	3-Furyl	H	O	OCH ₃	1:1	oil
2.92	Methyl	3-Furyl	H	O	OH	1:1	131-135
2.93	3-CP ₃ -benzyl	Phenyl	Methyl	O	OCH ₃	2:1	151-152
2.94	3-CP ₃ -benzyl	Phenyl	Methyl	O	OH	1:1	oil
2.95	2-Fluorobenzene	Phenyl	Methyl	O	OCH ₃	2:1	170-173
2.96	2-Fluorobenzene	Phenyl	Methyl	O	OH	1:0	160-162
2.97	2-Fluorobenzene	Phenyl	Methyl	O	OH	1:3	138-141
2.98	3-Fluorobenzyl	Phenyl	Methyl	O	OCH ₃	1:1	81-86
2.99	3-Fluorobenzyl	Phenyl	Methyl	O	OH	4:1	195-197
2.100	3-Fluorobenzyl	Phenyl	Methyl	O	ONa	3:1	250-260
2.101	4-Fluorobenzyl	Phenyl	Methyl	O	OCH ₃	1:1	112-115
2.102	4-Fluorobenzyl	Phenyl	Methyl	O	OH		

Use examples:

The herbicidal action of the 3-(het)arylcrotonic acid derivatives of the general formula I could be demonstrated by greenhouse experiments:

The culture vessels used were plastic flowerpots containing loamy sand with about 3.0% of humus as a substrate. The seeds of the test plant were sown separately according to species.

In the preemergence treatment, the active ingredients suspended or emulsified in water were applied directly after sowing by means of finely distributing nozzles. The vessels were lightly sprinkler-irrigated in order to promote germination and growth and were then covered with transparent plastic covers until the plants had begun to grow. This covering ensures uniform germination of the test plants, unless this has been adversely affected by the active ingredients.

For the postemergence application, the test plants are grown to a height of growth of from 3 to 15 cm, depending on the form of growth, before being treated with the active ingredients suspended or emulsified in water. For this purpose, the test plants are either sown directly and grown in the same vessels or first grown separately as seedlings and transplanted into the test vessels a few days before the treatment. The application rate for the postemergence treatment is 0.125 or 0.06 kg/ha of a.i.

The plants were kept at 10° to 25° C. or 20° to 35° C., according to species. The experimental period is extended over from 2 to 4 weeks. During this time, the plants were tended, and their reaction to the individual treatments was evaluated.

Evaluation was based on a scale from 0 to 100. 100 means no emergence of the plant or complete destruction of at least the aboveground parts and 0 means no damage or normal course of growth.

The plants used in the greenhouse experiments consisted of the following species:

Botanical Name	Common Name	Abbreviation
<i>Gossypium hirsutum</i>	Cotton	GOSHI
<i>Oryza sativa</i>	Rice	ORYSA
<i>Triticum aestivum</i>	Summer wheat	TRZAS
<i>Alopecurus myosuroides</i>	Slender foxtail	ALOMY
<i>Amaranthus retroflexus</i>	Redroot pigweed	AMARE
<i>Brachiaria platyphylla</i>	—	BRAPP
<i>Chenopodium album</i>	Common lambsquarters	CHEAL
<i>Sesbania exaltata</i>	Hemp sesbania	SEBEX
<i>Setaria faberii</i>	Giant foxtail	SETFA
<i>Setaria viridis</i>	Green foxtail	SETVI
<i>Solanum nigrum</i>	Black nightshade	SOLNI
<i>Veronica spp.</i>	Speedwell species	VERSS

The results listed in Table A show the superior herbicidal action and the better selectivity of the novel compound No. 2.2 in comparison with the comparative substance A disclosed in EP-A 409 368

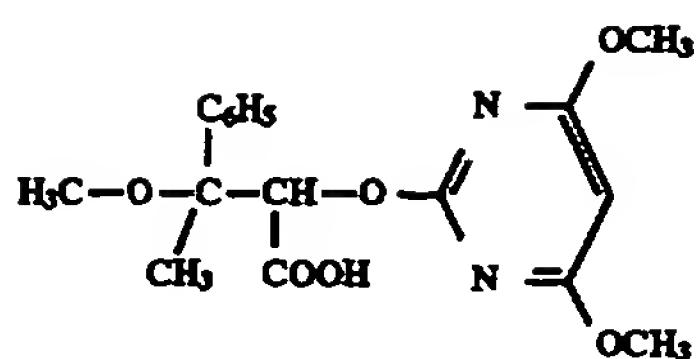
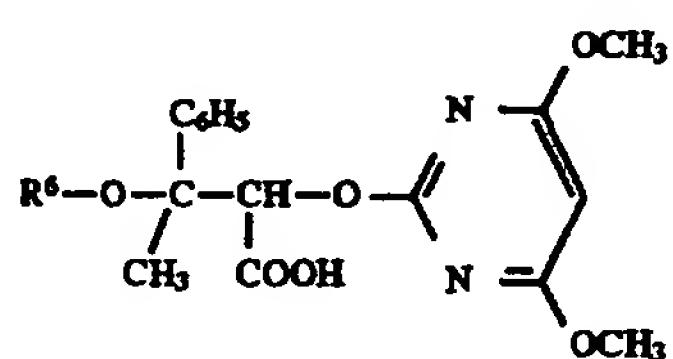


TABLE A

Examples of the control of undesirable plants and selectivity in the example crop cotton with postemergence application of 0.125 or 0.06 kg/ha of a.i. in the greenhouse.

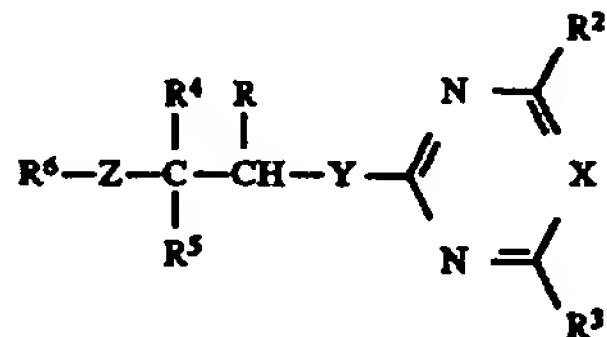


Example No.	Benzyl		CH ₃	
	2.2	Damage in %	A	Damage in %
Test	0.125 kg/ha	0.06 kg/ha	0.125 kg/ha	0.06 kg/ha
plants				
GOSHI	10	5	35	20
SEPTA	100	100	75	70
SETVI	100	98	80	60
AMARE	98	98	100	75
SOLNI	100	100	98	90

At application rates of 5 kg/ha to 0.25 kg/ha, compounds No. 2.84, 2.16, 2.52, 2.86 and 2.25 showed good herbicidal activity. Compounds No. 2.84 and 2.16 simultaneously showed very good selectivity in the example crop cotton. In addition, Example No. 2.16 was also selective in rice. Example 2.52 was well tolerated by the crop summer wheat.

We claim:

1. A 3-(het)arylcarboxylic acid derivative of the formula I



where R is formyl, CO₂H or a radical hydrolyzable to COOH and R₂ is halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy or C₁-C₄-alkylthio; X is nitrogen or CR¹⁴, where R¹⁴ is hydrogen or, together with R³, forms a 3-membered or 4-membered alkylene or alkenylene chain, in each of which a methylene group is replaced by oxygen; R³ is halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy or C₁-C₄-alkylthio or R³ is linked to R¹⁴ as stated above to form a 5-membered or 6-membered ring; R⁴ is phenyl or naphthyl which may be substituted by one or more, in particular one to three, of the following radicals: halogen, nitro, cyano, hydroxyl, mercapto, amino, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₁-C₄-alkylthio, C₁-C₄-alkylamino, di-C₁-C₄-alkylamino, C₁-C₄-alkylcarbonyl or C₁-C₄-alkoxycarbonyl;

a five-membered or six-membered heteroaromatic structure which contains one to three nitrogen atoms and/or one sulfur or oxygen atom and may carry one or more of the following radicals: halogen, nitro, cyano, hydroxyl, mercapto, amino, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₁-C₄-alkylthio, C₁-C₄-alkylamino, C₁-C₄-dialkylamino, C₁-C₄-alkylcarbonyl, C₁-C₄-alkoxycarbonyl or phenyl;

R⁵ is hydrogen, C₁-C₄-alkyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl, C₃-C₈-cycloalkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxyalkyl, C₁-C₄-alkylthioalkyl or phenyl;

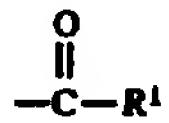
R⁶ is C₁-C₈-alkyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl or C₃-C₈-cycloalkyl, it being possible for these radicals to be mono- or polysubstituted in each case by: halogen, nitro, cyano, C₁-C₄-alkoxy, C₃-C₆-alkenyloxy, C₃-C₆-alkynyoxy, C₁-C₄-alkylthio, C₁-C₄-haloalkoxy, C₁-C₄-alkylcarbonyl, C₁-C₄-alkoxycarbonyl, C₁-C₄-alkylamino, di-C₁-C₄-alkylamino, phenyl or phenyl or phenoxy which is mono- or polysubstituted, for example mono- to trisubstituted, by halogen, nitro, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy or C₁-C₄-alkylthio;

Y is sulfur or oxygen or a single bond; and

Z is sulfur or oxygen;

with the proviso that R⁶ is not unsubstituted C₁-C₄-alkyl when R⁴ is unsubstituted phenyl, Z is oxygen and simultaneously R⁵ is methyl or hydrogen.

2. A 3-(het)arylcarboxylic acid derivative of the general formula I as claimed in claim 1, where R is



where R¹ has the following meanings:

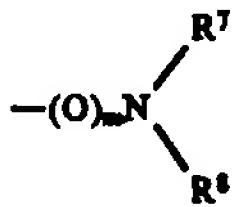
a) hydrogen;

b) a succinylimidoxy group;

c) a 5-membered heteroaromatic structure which is bonded via a nitrogen atom, contains two or three nitrogen atoms and may carry one or two halogen atoms or one or two of the following radicals:

C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy or C₁-C₄-alkylthio;

d) a radical



where m is 0 or 1 and R⁷ and R⁸, which may be identical or different, have the following meanings:

hydrogen;

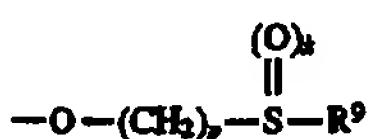
C₁-C₈-alkyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl or C₃-C₈-cycloalkyl, where each of these radicals may carry one to five halogen atoms or one or two of the following groups: C₁-C₄-alkoxy, C₃-C₆-alkenyloxy, C₃-C₆-alkynyoxy, C₁-C₄-alkylthio, C₃-C₆-alkenylthio, C₃-C₆-alkynylthio, C₁-C₄-haloalkoxy, C₁-C₄-alkylcarbonyl, C₃-C₆-alkenylcarbonyl, C₃-C₆-alkynylcarbonyl, C₁-C₄-alkoxycarbonyl, C₃-C₆-alkynyoxy carbonyl, di-C₁-C₄-alkylamino, C₃-C₈-cycloalkyl, phenyl or phenyl which is monosubstituted or polysubstituted by halogen, nitro, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy or C₁-C₄-alkylthio; phenyl which may be substituted by one or more of the following radicals: halogen, nitro, cyano, C₁-C₄-alkyl,

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C_1-C_4 -haloalkyl, C_1-C_4 -alkoxy, C_1-C_4 -haloalkoxy or C_1-C_4 -alkylthio;

R^7 and R^8 together form a cyclic, optionally substituted C_4-C_7 -alkylene chain or together form a cyclic, optionally substituted C_3-C_6 -alkylene chain containing a heteroatom selected from the group consisting of oxygen, sulfur and nitrogen;

c) R^1 is furthermore a group



where R^9 is C_1-C_4 -alkyl, phenyl or phenyl which is monosubstituted or polysubstituted by halogen, nitro, cyano, C_1-C_4 -alkyl, C_1-C_4 -haloalkyl, C_1-C_4 -alkoxy, C_1-C_4 -haloalkoxy or C_1-C_4 -alkylthio, or C_1-C_4 -haloalkyl, C_3-C_6 -alkenyl or C_3-C_6 -alkynyl, p may be 1, 2, 3 or 4 and k may be 0, 1 or 2;

f) a radical OR^{10} , where R^{10} is:

i) hydrogen, an alkali metal cation, one equivalent of an alkaline earth metal cation, the ammonium cation or an organic ammonium ion;

ii) C_3-C_6 -cycloalkyl which may carry one to three C_1-C_4 -alkyl radicals;

iii) C_1-C_6 -alkyl which may carry one to five halogen atoms or one of the following radicals:

C_1-C_4 -alkoxy, C_1-C_4 -alkylthio, cyano, C_1-C_4 -alkylcarbonyl, C_3-C_6 -cycloalkyl, C_1-C_4 -alkoxycarbonyl, phenyl, phenoxy or phenylcarbonyl, where the aromatic radicals in turn may each carry one to five halogen atoms or one to three of the following radicals: nitro, cyano, C_1-C_4 -alkyl, C_1-C_4 -haloalkyl, C_1-C_4 -alkoxy, C_1-C_4 -haloalkoxy or C_1-C_4 -alkylthio;

iv) C_1-C_6 -alkyl which may carry one to five halogen atoms and carries one of the following radicals: a 5-membered heteroaromatic structure containing one to three nitrogen atoms or a 5-membered heteroaromatic structure containing one nitrogen atom and one oxygen or sulfur atom, which may carry one to four halogen atoms or one or two of the following radicals: nitro, cyano, C_1-C_4 -alkyl, C_1-C_4 -haloalkyl, C_1-C_4 -alkoxy, C_1-C_4 -haloalkoxy or C_1-C_4 -alkylthio;

v) C_2-C_6 -alkyl which carries one of the following radicals in the 2 position: C_1-C_4 -alkoxyimino, C_3-C_6 -alkenyoxyimino, C_3-C_6 -haloalkenyoxyimino or benzylxyimino;

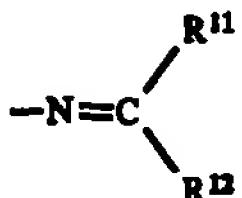
vi) C_3-C_6 -alkenyl or C_3-C_6 -alkynyl, where these groups in turn may carry one to five halogen atoms;

vii) phenyl which may carry one to five halogen atoms or one to three of the following radicals: nitro, cyano, C_1-C_4 -alkyl, C_1-C_4 -haloalkyl, C_1-C_4 -alkoxy, C_1-C_4 -haloalkoxy or C_1-C_4 -alkylthio;

viii) a 5-membered heteroaromatic structure which has bonded via a nitrogen atom, contains one to three nitrogen atoms and may carry one or two halogen atoms or one or two of the following radicals: nitro, cyano, C_1-C_4 -alkyl, C_1-C_4 -haloalkyl, C_1-C_4 -alkoxy, C_1-C_4 -haloalkoxy or C_1-C_4 -alkylthio;

26

ix) R^{10} is furthermore a group



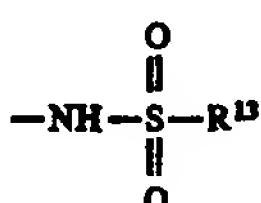
where

R^{11} and R^{12} , may be identical or different and are each:

10 C_1-C_6 -alkyl, C_3-C_6 -alkenyl, C_3-C_6 -alkynyl or C_3-C_6 -cycloalkyl, where these radicals may carry one C_1-C_4 -alkoxy or C_1-C_4 -alkylthio or one phenyl radical; phenyl which may be substituted by one or more of the following radicals:

15 halogen, nitro, cyano, C_1-C_4 -alkyl, C_1-C_4 -haloalkyl, C_1-C_4 -alkoxy, C_1-C_4 -haloalkoxy or C_1-C_4 -alkylthio; or R^{11} and R^{12} together form a C_3-C_{12} -alkylene chain which may carry one to three C_1-C_4 -alkyl groups;

20 g) or R^1 forms a radical



where R^{13} is:

C_1-C_4 -alkyl, C_3-C_6 -alkenyl, C_3-C_6 -alkynyl or C_3-C_6 -cycloalkyl, where these radicals may carry one C_1-C_4 -alkoxy or C_1-C_4 -alkylthio or one phenyl radical;

25 phenyl which may be substituted by one to five halogen atoms or one to three of the following radicals: nitro, cyano, C_1-C_4 -alkyl, C_1-C_4 -haloalkyl, C_1-C_4 -alkoxy, C_1-C_4 -haloalkoxy or C_1-C_4 -alkylthio.

30 3. A 3-arylcarboxylic acid derivative of the formula I as claimed in claim 1, in which R^4 is phenyl which may be substituted as stated in claim 1, and the remaining substituents have the meanings stated in claim 1.

35 4. A 3-arylcarboxylic acid derivative of the formula I as claimed in claim 1, in which Z is oxygen, R^4 is phenyl which may be substituted as stated in claim 1, R^5 is methyl, X is CH , R^2 and R^3 are each methoxy and Y , R^1 and R^6 have the meanings stated in claim 1.

40 5. A 3-hetarylcarboxylic acid derivative of the formula I as claimed in claim 1, in which R^4 is a five- or six-membered heteroaromatic structure as claimed in claim 1 and the remaining substituents have the meanings stated in claim 1.

45 6. A 3-hetarylcarboxylic acid derivative of the formula I as claimed in claim 1, in which Z is oxygen, R^4 is a five- or six-membered heteroaromatic structure as claimed in claim 1, R^5 is methyl, X is CH , R^2 and R^3 are methoxy and Y , R^1 and R^6 have the meanings stated in claim 1.

50 7. A herbicide containing a compound of the formula I as claimed in claim 1 and conventional inert additives.

55 8. A method for controlling undesirable plant growth, wherein a herbicidal amount of a compound of the formula I as claimed in claim 1 is allowed to act on the plants or on their habitat.

60 9. An agent for influencing plant growth, containing a compound of the formula I as claimed in claim 1 and conventional inert additives.

65 10. A method for regulating plant growth, wherein a bioregulatory amount of a compound of the formula I as claimed in claim 1 is allowed to act on the plants or on their habitat.

70 11. A 3-(het)arylcarboxylic acid derivative of the formula

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.: 5,703,017

DATED: December 30, 1997

INVENTOR(S): BAUMANN et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Abstract, cover page item [57], line 29, "C₃-C₄-" should be -- C₃-C₈ --.

Column 24, claim 2, line 65, "C₁-C₄-alkylthio" should be --C₁-C₄-alkylthio--.

Column 25, claim 2, line 26, "Which" should be --which--.

Signed and Sealed this
Third Day of March, 1998

Attest:



BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks

EXHIBIT

G

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

REQUEST FOR A CERTIFICATE OF CORRECTION UNDER RULE 1.322

Hon. Commissioner of Patents
& Trademarks
Washington, D.C. 20231

Sir:

In accordance with the provisions of Rule 1.322 of the Rules of Practice, which implement 35 USC 254, the Patent and Trademark Office is respectfully requested to issue a Certificate of Correction in the above-identified patent. Since the mistake with respect to the error in the patent is the fault of the Patent Office no fee is required. The desired correction in the patent is set forth in the attached form PTO 1050.

Favorable action on this request is respectfully solicited, and applicants ask that the corrections appear on all future copies of this patent.

Respectfully submitted,

KEIL & WEINKAUF

W. B. Keil

Herbert B. Keil
Reg. No. 18,967
Attorney for Applicants

1101 Connecticut Avenue, N.W.
Washington, D.C. 20036
(202) 659-0100

HBK/kas

January 14, 1998

ପ୍ରାଚୀନ ଭାଷାରେ ଶବ୍ଦ ଓ ପରିଚାର

22 22

Mary F. Allen / 1939

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.: 5,703,017

DATED: December 30, 1997

INVENTOR(S): BAUMANN et al.

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Column 25, claim 2, line 26, "Which" should be -which-.

MAILING ADDRESS OF SENDER:

Keil & Weinkauf
1101 Connecticut Avenue, N.W.
Suite 620
Washington, D.C. 20036

Patent No. 5,703,017

Form PTO 1050 (Rev. 2-93)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.: 5,703,017

DATED: December 30, 1997

INVENTOR(S): BAUMANN et al.

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Column 25, claim 2, line 26, "Which" should be --which--.

Signed and Sealed this
Third Day of March, 1998

Attest:



BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Ernst Baumann et al.

Patent No.: 5,703,017

Date of Patent: December 30, 1997

Entitled: 3(HET)ARYLCARBOXYLIC ACID DERIVATIVES,
THEIR PREPARATION AND INTERMEDIATES
FOR THEIR PREPARATION

Atty. Docket No.: 0050/043997

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

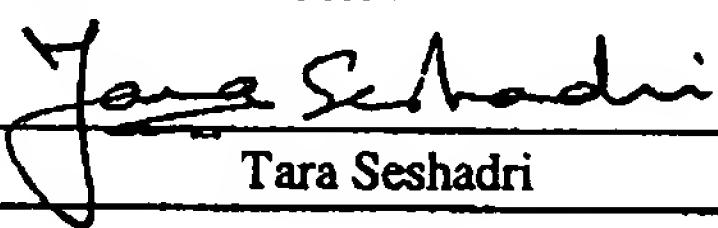
ATTN: Certificate of Correction Branch

CERTIFICATE OF MAILING BY "EXPRESS MAIL"

The undersigned hereby certifies that the correspondence listed below is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" Service under 37 CFR §1.10, postage prepaid, Express Mailing Label No. EQ 755812215 US, in an envelope addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date indicated below.

8/3/07

date of mailing and signature



Tara Seshadri

TRANSMITTAL LETTER

Sir/Madam:

Transmitted herewith are: Request for Certificate of Correction pursuant to 37 CFR 1.323 (in duplicate); Form PTO/SB/44 (in duplicate); Copy of Power of Attorney to Prosecute Applications Before the USPTO; Copy of Statement Under 37 CFR 3.73b; and An Acknowledgement Postcard to be filed in the above-identified patent application.

The Commissioner is hereby authorized to charge payment of any fees required in connection with the paper(s) transmitted herewith, or to credit any overpayment of same, to Deposit Account No. 010025. A duplicate copy of this transmittal letter is transmitted herewith.

Respectfully submitted,



Gayle B. O'Brien
Agent for Applicants
Reg. No. 48,812
Abbott Bioresearch Center
100 Research Drive
Worcester, MA 01605
(508) 688-8053

Date: August 3, 2007

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Ernst Baumann et al.

Patent No.: 5,703,017

Date of Patent: December 30, 1997

Entitled: 3(HET)ARYLCARBOXYLIC ACID DERIVATIVES,
THEIR PREPARATION AND INTERMEDIATES
FOR THEIR PREPARATION

Atty. Docket No.: 0050/043997

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

ATTN: Certificate of Correction Branch

CERTIFICATE OF MAILING BY "EXPRESS MAIL"

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8/3/07

date of mailing and signature



Tara Seshadri

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Gayle B. O'Brien
Agent for Applicants
Reg. No. 48,812
Abbott Bioresearch Center
100 Research Drive
Worcester, MA 01605
(508) 688-8053

Date: August 3, 2007

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Ernst Baumann et al.

Patent No.: 5,703,017

Date of Patent: December 30, 1997

Entitled: 3(HET)ARYLCARBOXYLIC ACID
DERIVATIVES, THEIR
PREPARATION AND
INTERMEDIATES FOR THEIR
PREPARATION

Atty. Docket No.: 0050/043997

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ATTN: Certificate of Correction Branch

REQUEST FOR CERTIFICATE OF CORRECTION PURSUANT TO 37 CFR 1.323

Sir/Madam:

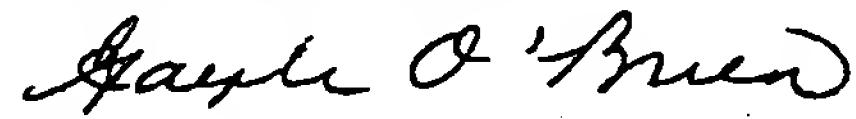
Applicant requests that the Commissioner issue a Certificate of Correction to correct the following typographical error in the above-referenced patent, all of which occurred due to a mistake on the part of the Patent Office:

Claim 13 should be amended to: insert "Y" before the phrase "is oxygen" at column 27, line 35.

The above-referenced "Y" was present in Applicant's original Claim 13. Thus, Applicant submits that the error occurred due to a mistake on the part of the Patent Office.

Applicant has enclosed Form PTO/SB/44 showing the necessary correction to the patent. Applicant believes that they do not owe a fee with this request. If, however, Applicant does owe a fee, the Commissioner is hereby authorized to charge the deficiency or overpayment to Deposit Account No. 01-0025. In addition, if there is ever any other fee deficiency or overpayment in connection with this patent, the Commissioner is hereby authorized to charge such deficiency or overpayment to Deposit Account No. 01-0025.

Respectfully submitted,



Date: August 3, 2007

Gayle B. O'Brien
Agent for Applicants
Reg. No. 48,812
Abbott Bioresearch Center
100 Research Drive
Worcester, MA 01605
(508) 688-8053

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTIONPage 1 of 1

PATENT NO. : 5,703,017

APPLICATION NO.: 08/537,843

ISSUE DATE : 30 December 1997

INVENTOR(S) : Ernst Baumann, et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

CLAIM 13

Column 27, line 35: insert "Y" before the phrase "is oxygen"

MAILING ADDRESS OF SENDER (Please do not use customer number below):
[ENTER ABBOTT COUNSEL NAME AND ADDRESS]

This collection of information is required by 37 CFR 1.322, 1.323, and 1.324. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1.0 hour to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Attention Certificate of Corrections Branch, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 1.73(b).

I hereby appoint:

Practitioner associated with the Customer Number:

OR

Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number
John D. Conway	39,150	Martin L. Katz	25,011
Gayle B. O'Brien	48,812		
Tara Seshadri	48,591		
David M. Steel	43,153		
Kenneth P. Zwicker	47,319		

as attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 1.73(b).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 1.73(b) to:

The address associated with Customer Number:

OR

<input checked="" type="checkbox"/> Firm or Individual Name:	Martin L. Katz		
Address	Citigroup Center - Suite 3800, 500 West Madison Street		
City	Chicago	State	IL
Country	USA	Zip	60661-2511
Telephone	312-375-1800	E-mail	mlkatz@codphillips.com

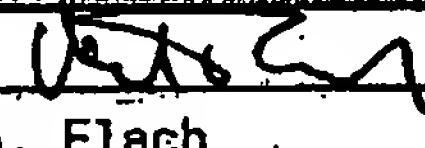
Assignee Name and Address:

ABBOTT GMBH & CO. KG
Max-Planck-Ring 3
65205 Wiesbaden GERMANY

A copy of this form, together with a statement under 37 CFR 1.73(b) (Form PTO/SB/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 1.73(b) may be completed by one of the practitioners appointed in this form if the appointed practitioner is authorized to act on behalf of the assignee, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature	ABBOTT GMBH & CO. KG		Date	August 3, 2007
Name	ppa. J. Bachmann	ppa. A. Flach	Telephone	+49-621-589-1775
Title	Senior Authorised Officers			

This collection of information is required by 37 CFR 1.31, 1.42 and 1.43. The information is required to obtain or retain a benefit by the public which is to the Government of the United States. Collection is authorized by 35 U.S.C. 122 and 37 CFR 1.1, Annex 1, et. al. This collection is estimated to take 2 minutes to complete. Appropriate fee is due to the USPTO. Amount will vary depending upon the individual case. Any comments on the amount of time you require to complete this form should be addressed to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

STATEMENT UNDER 37 CFR 3.73(b)Applicant/Patent Owner: Abbott GmbH & Co. KGApplication No./Patent No.: 5,703,017 Filed/Issue Date: December 30, 1997Entitled: 3-(HAT) arylcarboxylic acid derivatives, their preparation and intermediates for their preparation

Abbott GmbH & Co. KG, a Corporation
 (Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. the assignee of the entire right, title, and interest; or
2. an assignee of less than the entire right, title and interest
 (The extent (by percentage) of its ownership interest is _____ %)

In the patent application/patent identified above by virtue of either:

An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____ Frame _____, or for which a copy thereof is attached.

OR

A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

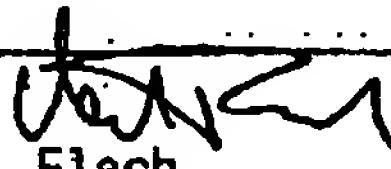
1. From: Inventory To: BASF Aktiengesellschaft
 The document was recorded in the United States Patent and Trademark Office at
 Reel 008091, Frame 0688, or for which a copy thereof is attached.
2. From: BASF Aktiengesellschaft To: Abbott GmbH & Co. KG
 The document was recorded in the United States Patent and Trademark Office at
 Reel 018454, Frame 0430, or for which a copy thereof is attached.
3. From: _____ To: _____
 The document was recorded in the United States Patent and Trademark Office at
 Reel _____, Frame _____, or for which a copy thereof is attached.

Additional documents in the chain of title are listed on a supplemental sheet.

As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

ABBOTT GmbH & Co. KGAugust 3, 2007J. Bachmann Signature 

Date

ppa. J. Bachmann ppa. A. Flach+49-621-589-1775

Printed or Typed Name

Telephone Number

Senior Authorised Officers

Title

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

RECEIVED IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
APPLICANT: Ernst Baumann et al.
PATENT NO.: 5,703,017
GRANT DATE: December 30, 1997
POR: 3-(Het) arylcarboxylic acid derivatives, their preparation and intermediates for their preparation
ATTORNEY DOCKET NUMBER: 0050/043997

The following have been received in the U.S. Patent Office on the date stamped hereon:

1. Transmittal Letter (in duplicate)
2. Request for Certificate of Correction
3. Form PTO/SB/44 (in duplicate)
4. Power of Attorney to Prosecute Applications Before the USPTO
5. Statement Under 37 CFR 3.73b

All mailed to the Patent and Trademark Office via Express Mail on: August 3, 2007
Express Mail Label No.: EO 755812215 US



Gayle O'Brien
Abbott Bioresearch Center
100 Research Drive
Worcester, MA 01605-4314

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**United States
Patent and
Trademark Office**

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Maintenance Fees Window Dates 07/30/2007 10:50 AM EDT

Patent Number: 5840722

Application Number: 08718377

	4th Year	8th Year	12th Year
Open Date	11/26/2001	11/25/2005	11/24/2009
Surcharge Date	05/28/2002	05/25/2006	05/25/2010
Close Date	11/25/2002	11/24/2006	11/24/2010

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[Return To:](#)[USPTO Home Page](#)[Finance Online Shopping Page](#)**United States
Patent and
Trademark Office**

Patent Maintenance Fees		07/30/2007 10:50 AM EDT	
Patent Number:	5840722	Application Number:	08718377
Issue Date:	11/24/1998	Filing Date:	09/30/1996
Window Opens:	11/24/2009	Surcharge Date:	05/25/2010
Window Closes:	11/24/2010	Payment Year:	
Entity Status:	LARGE		
Customer Number:	26474		
Street Address:	NOVAK DRUCE DELUCA & QUIGG, LLP		
City:	WASHINGTON		
State:	DC		
Zip Code:	20005		
Phone Number:	(202) 659-0100		
Currently there are no fees due.			

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EXHIBIT

H



Quintiles, Inc.
Post Office Box 9708
Kansas City, MO 64134-0708
(816) 767-6000

June 3, 2002

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

Subject: **Investigational New Drug Application
BSF 208075 for Pulmonary Arterial Hypertension**

**Serial No. 000
(Initial Submission)**

Dear Sir or Madam:

On behalf of Myogen, Inc., Quintiles, Inc. is submitting with this correspondence an initial Investigational New Drug Application (IND) for a new chemical entity, BSF 208075, an ETA selective endothelin receptor antagonist, being investigated in patients with pulmonary arterial hypertension. In accordance with 21 CFR Part 312 this thirty volume IND is submitted in triplicate.

To aid in the evaluation of the application, Section 10 of this IND contains additional information regarding communication with the Division of Cardio-Renal Drug Products that took place previously under IND 63,412. This includes a summary of the actions taken by Myogen in response to the Division's recommendations and copies of correspondence and meeting minutes that discussed the investigation of BSF 208075 for the indication of pulmonary arterial hypertension. In addition, Section 11 of this IND contains a copy of the informed consent form for protocol AMB-220, which is submitted in Section 6.

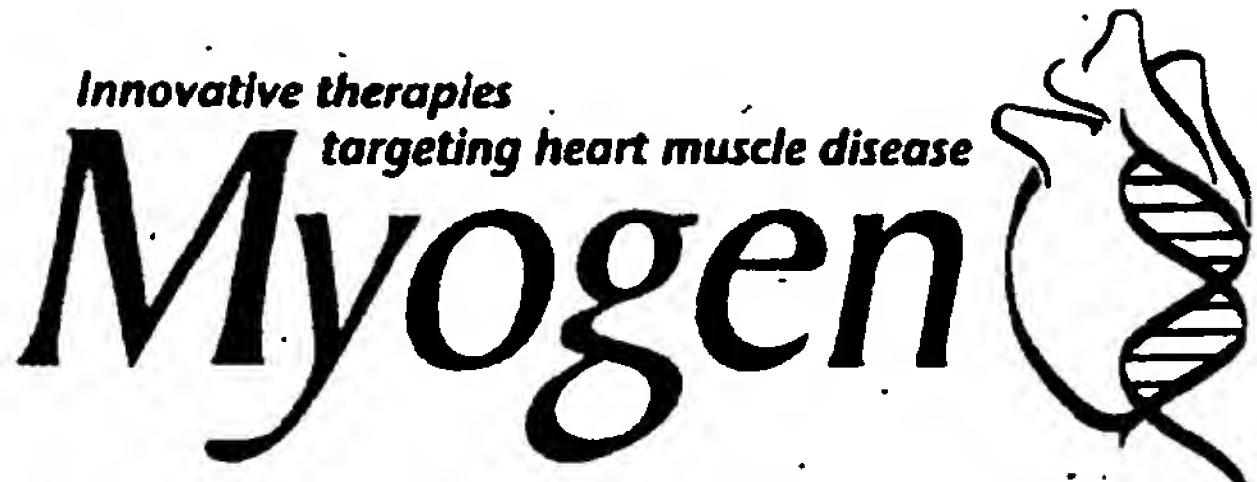
Also, please find enclosed for submission a letter from Myogen, Inc. transferring the responsibility as US Agent and Authorized Representative to Quintiles, Inc.; a letter from Quintiles accepting the transfer of responsibility; and an official Transfer of US Regulatory Obligations form delineating the duties being transferred.

Any questions concerning this Investigational New Drug Application should be directed to:

Marguerite Enlow, Pharm.D., RAC
Associate Regulatory Director,
Regulatory and Technical Services
Quintiles, Inc.
P.O. Box 9708
Kansas City, MO 64134-0708
Telephone: (816) 767-6408
Fax: (816) 767-7373

Sincerely,

Cynthia Kirk, Ph.D., RAC
Executive Director
Regulatory and Technical Services
Quintiles, Inc. Kansas City



June 3, 2002

Douglas Throckmorton, M.D.
Director, Division of Cardio-Renal Drug Products
Center for Drug Evaluation and Research (HFD-110)
Food and Drug Administration

Subject: BSF 208075
Selective Endothelin Receptor Antagonist
For Pulmonary Arterial Hypertension

General Correspondence:
Transfer of responsibility as
US Agent and Authorized
Representative

Dear Dr. Throckmorton:

Effective June 3, 2002, Myogen, Inc. is authorizing Quintiles, Inc., Kansas City, MO to act as its U.S. Agent and Authorized Representative for BSF 208075, an ETA Selective Endothelin Receptor Antagonist, being investigated in patients with pulmonary arterial hypertension. The duties to be performed by Quintiles, Inc. are:

- Submission of the IND
- Verbal and written interaction with the FDA
- Conduct of meetings with the FDA
- Submission of the IND annual reports
- Submission of IND amendments
- General IND maintenance

The contact person at Quintiles, Inc., is:

Marguerite Enlow, Pharm.D., RAC
Associate Regulatory Director,
Regulatory and Technical Services
Quintiles, Inc.
P.O. Box 9708
Kansas City, MO 64134-0708
Telephone: (816) 767-6408
Fax: (816) 767-7373

If you have any questions regarding the above information, please do not hesitate to contact me at Myogen, Inc., 7577 West 103rd Ave. #212, Westminster, CO 80021-5426, telephone (303) 464-5221.

Sincerely,

J. William Freytag
President, CEO and Chairman
Myogen, Inc.



Quintiles, Inc.
Post Office Box 9708
Kansas City, MO 64134-0708
(816) 767-6000

June 3, 2002

Douglas Throckmorton, M.D.
Director, Division of Cardio-Renal Drug Products
Center for Drug Evaluation and Research (HFD-110)
Food and Drug Administration

**Subject: BSF 208075
Selective Endothelin Receptor Antagonist
For Pulmonary Arterial Hypertension**

**General Correspondence:
Acceptance of responsibility
as US Agent and Authorized
Representative**

Dear Dr. Throckmorton:

Effective June 3, 2002, Quintiles, Inc., Kansas City, MO assumes the responsibility from Myogen, Inc. as the U.S. Agent and Authorized Representative for BSF 208075, an ETA Selective Endothelin Receptor Antagonist, being investigated in patients with pulmonary arterial hypertension. The duties to be performed by Quintiles, Inc. are:

- Submission of the IND
- Verbal and written interaction with the FDA
- Conduct of meetings with the FDA
- Submission of the IND annual reports
- Submission of IND amendments
- General IND maintenance

The contact person at Quintiles, Inc., is:

Marguerite Enlow, Pharm.D., RAC
Associate Regulatory Director,
Regulatory and Technical Services
Quintiles, Inc.
P.O. Box 9708
Kansas City, MO 64134-0708
Telephone: (816) 767-6408
Fax: (816) 767-7373

If you have any questions regarding the above information, please do not hesitate to contact me at Quintiles, Inc., P.O. Box 9708, Kansas City, Missouri 64134-0708, telephone (816) 767-6493.

Sincerely,

Cynthia Kirk, Ph.D., RAC
Executive Director
Regulatory and Technical Services
Quintiles, Inc. Kansas City

TRANSFER OF US FDA REGULATORY OBLIGATIONS FOR INVESTIGATIONAL
 PHARMACEUTICAL AND BIOLOGIC PRODUCTS UNDER AN INVESTIGATIONAL NEW DRUG (IND)
 APPLICATION (21 CFR 312.52)

Form No: CRO.FM.AMR.RA002.V02

Page 1 of 3

Sponsor:	Myogen	Project Code/ Work Order Number:	Not Assigned
Product Name:	BSF 208075	IND Number:	Not Available
Indication:	Pulmonary Arterial Hypertension	Protocol Number:	All protocols

Responsibility	21 CFR Reference	Obligation Assigned to:	
		Sponsor	Quintiles
A. 1. Preparation of all or part of an IND application	312.23	X	X
2. Submission of IND application to FDA		<input type="checkbox"/>	X
B. Maintain an IND with the following amendments, as necessary:			
1. Preparation of Protocol amendments (includes new protocols, changes in protocols, adding new investigators)	312.30	X	<input type="checkbox"/>
2. Preparation of Chemistry, Manufacturing, and Control amendments	312.31	X	<input type="checkbox"/>
3. Preparation of Pharmacology and Toxicology amendments	312.31	X	<input type="checkbox"/>
4. Preparation of Clinical amendments	312.31	X	<input type="checkbox"/>
5. Safety Reports (a) Preparation of initial report (b) Preparation of follow-up reports (c) Notifications to FDA (phone/fax or written) (d) Notifications to investigators	312.32	X X <input type="checkbox"/> X	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
6. Preparation of Annual Reports	312.33	X	X
7. Preparation of response to request for information or clinical hold	312.41, 42	X	X
8. Preparation of letter to withdraw an IND	312.38	X	X
9. Act as IND agent; submit all amendments to FDA	312.23 - 42	<input type="checkbox"/>	X
C. Selecting investigators and monitors			
1. Select qualified investigators ¹	312.53 (a)	X	<input type="checkbox"/>
2. Control of drug ¹ (a) Approve drug shipment after review of required information from investigator (including signed Form FDA 1572, CV) (b) Ship drug to approved investigators	312.53 (c) 312.53 (b)	X <input type="checkbox"/>	<input type="checkbox"/> X
3. Provide qualified monitors ¹	312.53 (d)	X	<input type="checkbox"/>

TRANSFER OF US FDA REGULATORY OBLIGATIONS FOR INVESTIGATIONAL
PHARMACEUTICAL AND BIOLOGIC PRODUCTS UNDER AN INVESTIGATIONAL NEW DRUG (IND)
APPLICATION (21 CFR 312.52)

Form No: CRO.FM.AMR.RA002.V02

Page 2 of 3

4. Informing investigators ¹			
(a) Review with investigators their regulatory responsibilities	312.60 -.69	X	<input type="checkbox"/>
(b) Supply investigator's brochure	312.55 (a)	X	<input type="checkbox"/>
(c) Inform investigators of new safety information about the study drug	312.55 (b)	X	<input type="checkbox"/>
D. Review of ongoing investigations	312.56		
1. Monitoring the investigation (includes ensuring that investigator is complying with all commitments in Section 9 of the signed Form FDA-1572) ¹	312.56(a)	X	<input type="checkbox"/>
2. Discontinue investigator participation if not compliant ¹ Note: If the sponsor does not discontinue an investigator who Quintiles believes to be significantly non-compliant, Quintiles will request a complete transfer of regulatory obligation for that site back to the sponsor.	312.56(b)	X	<input type="checkbox"/>
3. Initial evaluation of all adverse events ¹	312.56 (c)	X	<input type="checkbox"/>
4. Upon discontinuation of a study ¹ :	312.56 (d)	<input type="checkbox"/>	X
(a) Notify FDA		X	<input type="checkbox"/>
(b) Notify IRBs and investigators		X	<input type="checkbox"/>
(b) Assure disposition of drug from sites to sponsor		X	<input type="checkbox"/>
E. Recordkeeping and record retention	312.57		
1. Maintain sponsor records and reports for 2 years after study end <u>or</u> marketing application approved, for	312.57(a)(b)	<input type="checkbox"/>	<input type="checkbox"/>
(a) Records of drug shipment and disposition		X	<input type="checkbox"/>
(b) All correspondence with sponsor, FDA, IRB, investigators		X	<input type="checkbox"/>
(c) Records concerning adverse effects		X	<input type="checkbox"/>
(d) Other records required by FDA		X	<input type="checkbox"/>
2. Retain reserve samples of test articles and reference standards used in bioequivalence or bioavailability studies	312.57 (c)	X	<input type="checkbox"/>
F. Disposition of unused supply of investigational drug	312.59		
1. Assure return of drug from site to sponsor ¹		X	<input type="checkbox"/>
2. Conduct final disposition or destruction of drug ¹		X	<input type="checkbox"/>
G. If requested by FDA, submission of sponsor's records and reports to FDA for inspection	312.58 (a)	X	X
H. Apply for FDA approval to export investigational drug if:	312.110	<input type="checkbox"/>	<input type="checkbox"/>
(a) Drug is not approved for marketing in any country, AND			
(b) Drug is not under an active IND, AND			
(c) Drug is not being exported to one of listed countries ²			
X Not applicable			
I. Represent sponsor in resolution of disputes with FDA	312.48	X	X
J. Obtain investigator financial disclosure information	[FR 2/2/98]	X	<input type="checkbox"/>

Sponsor's name

Project code

TRANSFER OF US FDA REGULATORY OBLIGATIONS FOR INVESTIGATIONAL
PHARMACEUTICAL AND BIOLOGIC PRODUCTS UNDER AN INVESTIGATIONAL NEW DRUG (IND)
APPLICATION (21 CFR 312.52)

Form No. CRO.FM.AMR.RA002.V02

Page 3 of 3

¹ If responsibility for an item is shared between the sponsor and Quintiles, both boxes will be checked. Quintiles' responsibility for the item is limited to the list of sites attached to this document. This must be confirmed in the contract.

² Listed countries: Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, and current member nations of the European Union and European Economic Area.

According to 21 CFR 312.52(b), "A contract research organization that assumes any obligation of a sponsor shall comply with the specific regulations in this chapter applicable to this obligation and shall be subject to the same regulatory action as a sponsor for failure to comply with any obligation assumed under these regulations." The assignment of responsibility does not preclude either the sponsor or the CRO from participating in the requirements of the CFR.

The sponsor hereby transfers to Quintiles, Inc. the responsibilities indicated above under the column titled "Obligation Assigned to QUINTILES," effective Jan 18 2002 (date).

Sponsor: MYOGEN

J. William Freytag
Signature

J. William Freytag
Printed Name

President, CEO and Chairman
Title

1/18/02
Date

QUINTILES

Marguerite Enlow
Regulatory & Technical Services Signature

Marguerite Enlow
Printed Name

Associate Director
Title

1/18/02
Date

Sponsor's name
Project code

EXHIBIT

I

COPY



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 64,915

Myogen, Inc.
Attention: Mr. J. William Freytag
7575 West 103rd Avenue, Suite #102
Westminster, CO 80021

Dear Mr. Freytag:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 64,915

Sponsor: Myogen, Inc.

Name of Drug: BSF 208075

Date of Submission: June 3, 2002

Date of Receipt: June 4, 2002

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, on or before July 3, 2002, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies, we will notify you immediately that (1) clinical studies may not be initiated under this IND ("clinical hold") or that (2) certain restrictions apply to clinical studies under this IND ("partial clinical hold"). In the event of such notification, you must not initiate or you must restrict such studies until you have submitted information to correct the deficiencies, and we have notified you that the information you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports [21 CFR 312.33].

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, to either of the following addresses:

U.S. Postal Service:

Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, please call me at (301) 594-5333.

Sincerely yours,

Zelda McDonald
Regulatory Project Manager
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:

Quintiles, Inc.
Cynthia Kirk, Ph.D., RAC
P.O. Box 9708 (Dock 6, F3-M3026)
Kansas City, MO 64134-0708

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Zelda McDonald
6/10/02 02:21:20 PM

EXHIBIT

J



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-081

Gilead Colorado, Inc.
Attention: Ms. Linnea Tanner
Director, Regulatory Affairs
7575 West 103rd Ave., #102
Westmister, CO 80021-5426

Dear Ms. Tanner:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Letairis (ambrisentan) 5 and 10 mg Tablets

Date of Application: December 13, 2006

Date of Receipt: December 18, 2006

Our Reference Number: NDA 22-081

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 16, 2007 in accordance with 21 CFR 314.101(a).

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

RECEIVED

JAN 17 2005

Per 101

If you have any questions, please contact:

Ms. Melissa Robb
Regulatory Health Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Edward Fromm

1/10/2007 02:31:37 PM

EXHIBIT

K

REGULATORY REVIEW PERIOD ACTIVITIES

The table below summarizes representative formal submissions and contacts between the drug sponsor and FDA throughout the regulatory review period. The table is not comprehensive as to every event corresponding to a given type of submission, nor does it reflect regular email and telephone contacts throughout the regulatory review period to discuss upcoming submissions and provide preliminary information. Following the table below is a more comprehensive list of regulatory review activities.

2002-06-03	Initial submission date of IND No. 64,915
2002-06-04	Receipt date of IND No. 64,915
2002-06-28	Revised informed consent form
2002-07-17	Updated information for drug substance and drug product
2002-08-30	Clinical protocol amendment
2002-10-29	Response to request for information – CMC
2002-11-06	Information amendment: clinical
2002-12-09	Response to request for information: 26 wk. animal toxicity studies
2003-01-02	Rationale & study summary for additional long-term protocol
2003-01-13	Response to request for additional information regarding IND
2003-01-14	Response to request re safety monitoring plans for clinical trial
2003-02-07	Protocol amendment: new protocol
2003-03-05	IND 15-Day ADR Report
2003-03-11	Investigator notification of IND safety report for elevated liver function tests
2003-04-01	Duration of chronic toxicity study
2003-05-02	IND safety report: follow-up
2003-05-15	Type B meeting request
2003-05-15	Fax requesting End of Phase II meeting
2003-08-05	Information package for 27 August 2003 meeting
2003-08-27	End of Phase II meeting with FDA
2003-10-08	New Phase III protocols
2003-12-02	Change in clinical protocol
2003-12-18	Request for special protocol assessment 2-year mouse carcinogenicity protocol
2004-02-13	Information amendment
2004-03-17	Pharmacology-toxicology 2-Year rat and mouse final protocols

2004-03-25 Type C meeting request
2004-05-06 Protocol amendments
2004-05-27 Orphan drug application: amendment
2004-08-09 Type C meeting request to discuss proposed changes to the ambrisentan program
2004-08-27 Initial written report: 15-day safety alert report
2004-09-27 Type C meeting information package
2004-10-13 Meeting
2004-12-07 Information amendment: pharmacology/toxicology: 2-year rat and mouse carcinogenicity
2005-02-15 New protocol
2005-03-09 Information amendment: pharmacology/toxicology: 2-year rat and mouse carcinogenicity studies
2005-04-05 Response to request for information
2005-04-12 Protocol amendment
2005-05-24 Converting ARIES-2 study sites to ARIES-1
2005-08-04 Information amendment: Chemistry, Manufacturing and Controls
2005-08-22 Data analysis plan for FDA feedback
2005-08-22 Fax re 7 day safety report - initial manufacturer's report
2005-08-25 IND safety reports
2005-09-07 Request for FDA review of QT/QTc study proposal
2005-09-12 Type C meeting request: development plan for biopharmaceutics and clinical pharmacology
2005-10-04 Information amendment: Chemistry, Manufacturing, and Controls
2005-10-04 IND safety report: follow-up to a written report
2005-10-13 Meeting re PK and clinical pharmacology
2005-10-18 New protocol and new investigator
2005-10-19 Teleconference re data analysis plans
2005-11-04 New protocol and new investigator
2005-11-07 Response to FDA comments on QT/QTc study design
2005-11-11 Protocol amendment: change in protocol
2005-11-11 Information amendment: pharmacology/toxicology 2-year rat and mouse carcinogenicity studies
2005-11-29 Data analysis plans
2005-11-29 Information amendment: pharmacology/toxicology
2005-11-30 Data analysis plan for population pharmacokinetic modeling
2005-11-30 Protocol: new protocol and new investigator
2005-11-30 Data analysis plans

2005-12-15 Teleconference re PK/PD development plans
2005-12-19 IND safety report: initial written report
2005-12-19 Protocol amendment: new protocol and new investigators
2006-01-09 IND safety report: follow-up to a written report
2006-01-13 Protocol amendment: change in protocol
2006-01-16 IND safety report: follow-up to a written report
2006-01-23 Protocol amendment: change in protocol
2006-01-27 IND safety report: follow-up to a written report
2006-02-09 Request for fast track designation
2006-02-21 Response to IND correspondence
2006-03-02 IND safety report: follow-up to a written report
2006-03-08 Type B meeting request: Pre-NDA
2006-03-15 Requirements and format of NDA
2006-03-23 Information amendment: pharmacology/toxicology
2006-04-19 Information amendment: pharmacology/toxicology
2006-04-21 Pre-NDA briefing document
2006-04-27 IND safety report: initial written report
2006-05-04 Information amendment: pharmacology/toxicology
2006-05-08 Response to FDA comments
2006-05-17 Type B meeting request: pre-NDA CMC
2006-05-19 Pre-NDA meeting
2006-05-26 IND safety report: follow-up to a written report
2006-06-02 IND safety report: initial written report
2006-06-14 Request feedback on non-clinical NDA format and content
2006-06-15 Information amendment: clinical CSR's
2006-06-28 CMC pre-NDA information package
2006-07-06 IND safety report: initial and follow-up written safety report
2006-07-26 Pre-NDA CMC meeting
2006-10-06 CMC- proposed commercial dissolution method
2006-10-13 Proposal for 4-month safety update
2006-10-30 IND safety report: follow-up to a written report
2006-11-07 IND safety report: follow-up to a written report
2006-11-28 IND safety report: follow-up to a written report
2006-12-07 Transfer of sponsorship
2006-12-13 Submission of NDA No. 22-081
2006-12-18 Receipt of NDA No. 22-081
2007-01-09 Teleconference

2007-01-18	Response to letter re submission of complete CRF's and filing process
2007-01-19	Telephone call regarding inspections at clinical sites that conducted Phase 3 studies
2007-01-22	Email regarding revised protocol document-presence of sponsors
2007-02-09	Teleconference re protocols for capturing lab values
2007-02-13	Response to questions on the distribution of ambrisentan and RiskMAP
2007-02-15	IND safety report: follow-up to a written report
2007-03-03	Request for meeting to discuss status of review of NDA 22-081. Update on Amendments submitted to NDA
2007-03-07	Unformatted prescribing information; option to resolve formatting
2007-03-20	FDA site inspection
2007-03-20	Response regarding request for efficacy & safety datasets
2007-03-21	IND safety report: initial written report
2007-03-22	Protocol amendment: change to protocol
2007-03-29	90-day teleconference
2007-04-03	Request for Meeting to discuss dosing interval
2007-04-10	Protocol amendment: new protocol and new investigator
2007-04-16	Response to questions regarding dissolution profiles
2007-04-19	Population pharmacokinetic (PK) data analysis plan (DAP) amendment
2007-04-19	Response to questions regarding bioanalytical assay issues
2007-04-23	Response regarding randomization
2007-04-24	Protocol amendment: change to protocol
2007-04-30	IND safety report: follow up to a written safety report
2007-05-02	Protocol amendment. New protocol and new investigator
2007-05-04	DDMAC promotional materials. Request for perspective review and advisory comments for product launch materials
2007-05-08	Protocol amendment: change to protocol
2007-05-25	IND safety report: follow up to a written safety report
2007-05-25	Meeting
2007-05-31	Proposed pediatric study request
2007-05-31	IND safety report: follow-up to a written report
2007-06-07	Protocol amendment: new investigators
2007-06-07	IND safety report: follow-up to a written report
2007-06-15	Marketing approval letter for NDA 22-081



Back to Main TOC

Product ID	Department	Country	Document Date	Book Number	Document Type	Document Title	Keywords
<h2>Ambrisentan: Pulmonary Arterial Hypertension - IND 64,915</h2>							
1	Regulatory	US	7/20/2007	Temp 110	FDA Submission - IND	IND Safety Report. Initial Written Report. S-199	64,915
1	Regulatory	US	7/10/2007	Temp 110	FDA Submission - IND	IND Safety Report. Follow-up to a Written Report. S-198	64,915
1	Regulatory	US	6/28/2007	Temp 113	FDA Submission - IND	Annual Report. S-197	64,915
1	Regulatory	US	6/22/2007	Temp 110	FDA Submission - IND	IND Safety Report. Initial Written Report. S-196	64,915
1	Regulatory	US	6/18/2007	Temp 110	FDA Submission - IND	IND Safety Report. Follow-up to a Written Report. S-195	64,915
1	Regulatory	US	6/18/2007	Temp 110	FDA Submission - IND	IND Safety Report. Initial Written Report. S-194	64,915
1	Regulatory	US	6/7/2007	Temp 110	FDA Submission - IND	IND Safety Report. Follow-up to a Written Report. S-193	64,915
1	Regulatory	US	6/7/2007	Temp 110	FDA Submission - IND	Protocol Amendment. New Investigators. S-192	64,915
1	Regulatory	US	5/31/2007	Temp 110	FDA Submission - IND	IND Safety Report. Follow-up to a Written Report. S-191	64,915
1	Regulatory	US	5/31/2007	Temp 110	FDA Submission - IND	Other. Proposed Pediatric Study Request. S-190	64,915
1	Regulatory	US	5/29/2007	Temp 110	FDA Submission - IND	IND Safety Report. Follow-up to a Written Report. S-189	64,915
1	Regulatory	US	5/25/2007	Temp 110	FDA Submission - IND	IND Safety Report. Follow-up to a Written Report. S-188	64,915
1	Regulatory	US	5/18/2007	Temp 110	FDA Correspondence - Letter (Fax)	L. Tanner/N. Stockbridge - The 7 Day Safety Report	2007-05-18_64915_CORR LETTER_FAX_LTANNER_R_NSTOCKBRIDGE.pdf
1	Regulatory	US	5/18/2007	Temp 110	FDA Correspondence - Email	L. Tanner/D. Brum - Email with the 7-day Safety Report Documents attachment.	2007-05-18_64915_CORR_EMAIL_DBRUM_LTANNER_ER.pdf
1	Regulatory	US	5/18/2007	Temp 110	FDA Submission - IND	IND Safety Report. Initial Written Report. S-187	64,915

1	Regulatory	US	5/14/2007	Temp 110	FDA Submission - IND	IND Safety Report. Initial Written Report. S-186	S-186	64,915
1	Regulatory	US	5/8/2007	Temp 112	FDA Submission - IND	Protocol Amendment. Change to Protocol: Addendum to Protocol(s) AMB-320/321-E, AMB-222 and AMB-220-E. S-185	S-185	64,915
1	Regulatory	US	5/2/2007	Temp 110	FDA Submission - IND	Protocol Amendment. New Protocol and New Investigator. S-184		64,915
1	Regulatory	US	4/30/2007	Temp 110	FDA Submission - IND	IND Safety Report. Follow-up to a Written Report. S-183	S-183	64,915
1	Regulatory	US	4/27/2007	Temp 110	FDA Submission - IND	IND Safety Report. Follow-up to a Written Report. S-182	S-182	64,915
1	Regulatory	US	4/26/2007	Book 109	FDA Submission - IND	Protocol Amendment. New Investigators. S-181	S-181	64,915
1	Regulatory	US	4/24/2007	Book 109	FDA Submission - IND	Protocol Amendment. Change to Protocol: Replacement of Amendment No. 1.0 to Protocol AMB-323. S-180	S-180	64,915
1	Regulatory	US	4/11/2007	Book 109	FDA Submission - IND	IND Safety Report - Initial Written Report. S-179	S-179	64,915
1	Regulatory	US	4/10/2007	Book 109	FDA Submission - IND	Protocol Amendment. New Protocol and New Investigator. S-178	S-178	64,915
1	Regulatory	US	4/4/2007	Book 109	FDA Submission - IND	IND Safety Report. Follow-up to a Written Report. S-177	S-177	64,915
1	Regulatory	US	3/22/2007	Temp 111	FDA Submission - IND	Protocol Amendment. Change to Protocol: Amendment No. 1 to Protocol AMB-323. S-176	S-176	64,915
1	Regulatory	US	3/21/2007	Book 109	FDA Submission - IND	IND Safety Report. Initial Written Report. S-175	S-175	64,915
1	Regulatory	US	2/23/2007	Book 109	FDA Submission - IND	Protocol Amendment. New Investigators. S-174	S-174	64,915
1	Regulatory	US	2/23/2007	Book 109	FDA Submission - IND	IND Safety Report. Follow-up to a Written Report. S-173	S-173	64,915
1	Regulatory	US	2/23/2007	Book 109	FDA Submission - IND	IND Safety Report. Initial Written Report. S-172	S-172	64,915
1	Regulatory	US	2/15/2007	Book 109	FDA Submission - IND	IND Safety Report. Follow-up to written Report. S-171	S-171	64,915

1	Regulatory	US	2/2/2007	Book 109	FDA Correspondence - Email	E.Smith/L.Tanner - Following on Transfer of Sponsorship from Myogen to Gilead, Sciences	02_64915_CORR_EMAIL_ESMITH_LTAN_NER.pdf	64,915
1	Regulatory	US	1/30/2007	Book 109	FDA Submission - IND	IND Safety Report. Initial Written Report. S-170	S-170	64,915
1	Regulatory	US	1/30/2007	Book 109	FDA Submission - IND	Protocol Amendment. New Investigators. S-169	S-169	64,915
1	Regulatory	US	1/30/2007	Book 109	FDA Submission - IND	Protocol Amendment. New Investigators. S-169 [REDACTED] and New Investigators. S-169	S-169	64,915
1	Regulatory	US	1/30/2007	Book 109	FDA Submission - IND	Protocol Amendment. New Investigators. S-169	S-169	64,915
1	Regulatory	US	1/19/2006	Book 83	FDA Submission - IND	Protocol Amendment. New Investigators. S-167	S-167	64,915
1	Regulatory	US	12/15/2006	Book 83	FDA Correspondence - Letter	E.Fromm/L.Tanner. FDA Letter - Acknowledgment of the sponsor change.	2006-12-15_64915_CORR LETTER_EFROMM_LTANNER.pdf	64,915
1	Regulatory	US	12/12/2006	Book 83	FDA Correspondence - Phone	L.Tanner/M.Robb. FDA contact report (phone call) - Clarify process for liaison with the Division during the review of NDA 022-081 and for submitting responses to reviewer questions.	2006-12-12_64915_CORR_PHONE_MROBB_LTAN_NER.pdf	64,915
1	Regulatory	US	12/8/2006	Book 83	FDA Correspondence - Letter	N.Stockbridge/L.Tanner. FDA Letter indicates that Division does not recommend use of proprietary name LETAIRIS.	08_64915_CORR LETTER_NSTOCKBRIDGE_LTANNER.pdf	64,915
1	Regulatory	US	12/7/2006	Book 83	FDA Correspondence - Letter	N.Stockbridge/L.Tanner. FDA Letter - Clarification to Requirements 120-day Safety Update	07_64915_CORR LETTER_NSTOCKBRIDGE_LTANNER.pdf	64,915
1	Regulatory	US	12/7/2006	Book 83	FDA Submission - IND	Other. Transfer of Sponsorship. S-165	S-166	64,915
1	Regulatory	US	12/6/2006	Book 83	FDA Correspondence - Phone	L.Tanner/M.Robb - Confirm status of submission of NDA and transfer of sponsorship from Myogen to Gilead Sciences, Inc.	06_64915_CORR_PHONE_MROBB_LTAN_NER.pdf	64,915
1	Regulatory	US	11/28/2006	Book 83	FDA Submission - IND	IND Safety Report. Follow-up to a Written Safety Report. S-165	S-165	64,915
1	Regulatory	US	11/20/2006	Book 83	FDA Submission - IND	Protocol Amendment. New Investigators. S-164	S-164	64,915
1	Regulatory	US	11/20/2006	Book 83	FDA Submission - IND	IND Safety Report. Follow-up to a Written Safety Report. S-163	S-163	64,915

1	Regulatory	US	11/7/2006	Book 83	FDA Submission - IND	IND Safety Report. Follow-up to a Written Safety Report. S-162	S-162	64,915
1	Regulatory	US	10/30/2006	Book 83	FDA Submission - IND	IND Safety Report. Follow-up to a Written Safety Report. S-161	S-161	64,915
1	Regulatory	US	10/24/2006	Book 83	FDA Correspondence - Phone	L. Tanner/M.Robb - Confirm how RiskMAP materials are regulated and obtain status of review of trademark.	24_64915_CORR_PHONE_LTANNER_MR_OBB_.pdf	64,915
1	Regulatory	US	10/20/2006	Book 83	FDA Submission - IND	Protocol Amendment. New Investigators. S-160	S-160	64,915
1	Regulatory	US	10/20/2006	Book 83	FDA Correspondence - Email	L. Tanner/M.Robb - FDA contact report (e-mail) - Proposal for 4-month Safety Update to NDA, S-159	20_64915_CORR_EMAIL_LTANNER_MRO_BB_.pdf	64,915
1	Regulatory	US	10/16/2006	Book 83	FDA Correspondence - Email	L. Tanner/M.Robb - FDA contact report (e-mail) that confirms that the word version of the PI needs to be submitted in the two-column format.	16_64915_CORR_EMAIL_LTANNER_MRO_BB_.pdf	64,915
1	Regulatory	US	10/13/2006	Book 83	FDA Submission - IND	Other: Proposal for 4-Month Safety Update. S-159	S-159	64,915
1	Regulatory	US	10/12/2006	Book 83	FDA Correspondence - Email	L. Tanner/M.Rabb. Email with two attachments. Clarification on Format of PI, 1\vs. 2 Column Format for the PI; Ambrisentan.	12_64915_CORR_EMAIL_LTANNER_MRO_BB_.pdf	64,915
1	Regulatory	US	10/10/2006	Book 83	FDA Correspondence - Email	Email from T.Marshall to S. Goldie with the attachment - electronic Desk Copy of AMB S-157: New Commercial Drug Product Dissolution Method.	10_64915_CORR_EMAIL_TMARSHALL_S_GOLDIE_.pdf	64,915
1	Regulatory	US	10/9/2006	Book 83	FDA Submission - IND	IND Safety Report. Initial and Follow-up Written Report. S-158	S-158	64,915
1	Regulatory	US	10/6/2006	Book 83	FDA Submission - IND	Other: CMC - Proposed Commercial Dissolution Method. S-157	S-157	64,915
1	Regulatory	US	10/4/2006	Book 83	FDA Correspondence - Email	Email from M. Robb to L. Tanner. Subject: Pediatric exclusivity, Orphan Drugs; Ambrisentan - ND 22-081.	04_64915_CORR_EMAIL_LTANNER_MRO_BB_.pdf	64,915

1	Regulatory	US	10/4/2006	Book 83	FDA Correspondence - Phone	M.Robb/L.Tanner. Purpose: Confirm location for providing the statement that ambrisentan is exempt from the requirement for submitting pediatric data in the NDA.	2006-10-04_64915_CORR_PHONE_MROBB_LTAN_NER_.pdf	64,915
1	Regulatory	US	9/27/2006	Book 83	FDA Correspondence - Phone	M.Robb/L.Tanner. Purpose: Confirm timing for the submission of NDA.	2006-09-27_64915_CORR_PHONE_MROBB_LTAN_NER_.pdf	64,915
1	Regulatory	US	9/26/2006	Book 82	FDA Submission - IND	Protocol Amendment. New Investigators. S-156	2006-08-21_64915_CORR_EMAIL_USERFEESFDA_HISOKOSKI_.pdf	64,915
1	Regulatory	US	9/12/2006	Book 82	FDA Submission - IND	IND Safety Report. Initial and Follow-up Written Report. S-155	2006-08-08_64915_CORR_PHONE_MROBB_LTAN_NER_2_.pdf	64,915
1	Regulatory	US	9/6/2006	Book 82	FDA Submission - IND	Protocol Amendment AMB-323. New Investigators. S-154	2006-08-08_64915_CORR_PHONE_MROBB_LTAN_NER_2_.pdf	64,915
1	Regulatory	US	8/23/2006	Book 82	FDA Correspondence - Letter - Meeting Minutes	Letter from S.Goldie/T.Marshall Meeting Minutes - Pre-NDA CMC meeting with FDA.	2006-08-23_64915_CORR_MEETING_MINUTES.pdf	64,915
1	Regulatory	US	8/21/2006	Book 82	FDA Correspondence - Email	Email from the FDA User Fee System	2006-08-21_64915_CORR_EMAIL_USERFEESFDA_HISOKOSKI_.pdf	64,915
1	Regulatory	US	8/8/2006	Book 82	FDA Correspondence - Phone	L.Tanner/M.Robb. Call at 2:30 PM. Purpose: Confirm Format of Annotating Prescribing Information.	2006-08-08_64915_CORR_PHONE_MROBB_LTAN_NER_2_.pdf	64,915
1	Regulatory	US	8/8/2006	Book 82	FDA Correspondence - Phone	L.Tanner/M.Robb. Call at 8:30AM Purpose: Confirm format of annotating the prescribing information based on the new requirements.	2006-08-08_64915_CORR_PHONE_MROBB_LTAN_NER_2_.pdf	64,915
1	Regulatory	US	7/26/2006	Book 82	FDA Correspondence - Mating Minutes	T.Marshall. Myogen Pre-NDA CMC Meeting Minutes for July 26, 2006.	2006-07-26_64915_CORR_MEETING_MINUTES.pdf	64,915
1	Regulatory	US	7/25/2006	Book 82	FDA Submission - IND	Protocol Amendment. New Investigators. S-153	2006-07-24_64915_CORR_EMAIL_TMARSHALL_S_GOLDIE_1_.pdf	64,915
1	Regulatory	US	7/24/2006	Book 82	FDA Correspondence - Email	T.Marshall/S.Goldie. FDA Pre- meeting Responses to Myogen's Pre- NDA CMC Meeting Questions.	2006-07-24_64915_CORR_EMAIL_TMARSHALL_S_GOLDIE_.pdf	64,915
1	Regulatory	US	7/24/2006	Book 82	FDA Correspondence - Email	T.Marshall/S.Goldie. Pre-NDA CMC Meeting - Additional Attendees.	2006-07-24_64915_CORR_EMAIL_TMARSHALL_S_GOLDIE_.pdf	64,915
1	Regulatory	US	7/17/2006	Book 82	FDA Submission - IND	IND Safety Report. Follow-up to a Written Safety Report. S-152	S-152	64,915

1	Regulatory	US	7/13/2006	Book 82	FDA Correspondence - Phone	H.Isokoski/B.Friedman. NDA Number for Ambisentan.	2006-07-12_64915_CORR_PHONE_HISOKOSKI_BF_RIEDMAN_.pdf	64,915
1	Regulatory	US	7/6/2006	Book 82	FDA Correspondence - Email	L.CURRAN/ESUB/FDA. To clarify issues to which there is no apparent guidance.	2006-07-06_64915_CORR_EMAIL_ESUB_LCURRA_N.pdf	64,915
1	Regulatory	US	7/6/2006	Book 82	FDA Submission - IND	IND Safety Report. Follow-up to a Written Safety Report. S-151		64,915
1	Regulatory	US	6/30/2006	Book 107-108	FDA Submission - IND	Annual Report. S-150		64,915
1	Regulatory	US	6/28/2006	Book 106	FDA Submission - IND	Other. CMC Pre-NDA Information Package S-149		64,915
1	Regulatory	US	6/20/2006	Book 82	FDA Submission - IND	Information Amendment. Update to Investigator 1572 Forms. S-148		64,915
1	Regulatory	US	6/20/2006	Book 82	FDA Correspondence - Phone	L.Tanner/M.Rabb. Feedback on proposed plan for submitting carcinogenicity data to the NDA (IND Serial No. 145).	2006-06-20_64915_CORR_PHONE_MROBB_LTAN_NER_.pdf	64,915
1	Regulatory	US	6/20/2006	Book 105	FDA Submission - IND	Information Amendment. New Protocol and New Investigator. S-147		64,915
1	Regulatory	US	6/15/2006	Book 100-104	FDA Submission - IND	Information Amendment - Clinical CSRs AMB-105 and AMB-106. S-146		64,915
1	Regulatory	US	6/14/2006	Book 82	FDA Correspondence - Phone	Phone. T.Marshall/S.Goldie regarding Pre-NDA CMC Meeting. Scheduling Submission of Pre-NDA CMC meeting information.	2006-06-14_64915_CORR_PHONE_SGOLDIE_TMA_RSHALL.pdf	64,915
1	Regulatory	US	6/14/2006	Book 82	FDA Correspondence - Email	Email from L.Tanner/M.Robb - Request for feedback: IND64,915 S-145.	2006-06-14_64915_CORR_EMAIL_LTANNER_MRO_BB.pdf	64,915
1	Regulatory	US	6/14/2006	Book 82	FDA Submission - IND	Other. Request Feedback on Nonclinical NDA Format and Content. S-145		64,915
1	Regulatory	US	6/12/2006	Book 82	FDA Submission - IND	IND Safety Report. Initial and Follow-up Written Report. S-144		64,915
1	Regulatory	US	6/7/2006	Book 82	FDA Submission - IND	IND Safety Report. Initial Written Report. S-143		64,915
1	Regulatory	US	6/1/2006	Book 82	FDA Submission - IND	Information Amendment. Update to Investigator 1572 Forms. S-142		64,915

1	Regulatory	US	5/26/2006	Book 82	FDA Correspondence - Letter	Letter from S.Goldie/T.Marshall regarding Pre-NDA CMC meeting with FDA.	2006-05-26_64915_CORR LETTER SGOLDIE_TMARSHALL.pdf	64,915
1	Regulatory	US	5/26/2006	Book 82	FDA Correspondence - Fax	Fax from M.Robb/L.Tanner - Meeting Minutes from Pre-NDA meeting with FDA on May 19, 2006.	2006-05-26_64915_CORR_FAX_MROBB_LTANNER.pdf	64,915
1	Regulatory	US	5/26/2006	Book 82	FDA Submission - IND	IND Safety Report. Follow-up to a Written Report. S-141	S-141	64,915
1	Regulatory	US	5/25/2006	Book 82	FDA Correspondence - Email	S.Goldie/T.Marshall. Contract Information.	2006-05-25_64915_CORR EMAIL_TMARSHALL_SGOLDIE.pdf	64,915
1	Regulatory	US	5/25/2006	Book 82	FDA Correspondence - Phone	Phone call - T.Marshall/S.Goldie regarding Pre-NDA CMC meeting request.	2006-05-25_64915_CORR_PHONE_SGOLDIE_TMARSHALL.pdf	64,915
1	Regulatory	US	5/19/2006	Book 82	FDA Correspondence - Phone	Phone call - T.Marshall/M.Robb regarding Pre-NDA CMC meeting request.	2006-05-19_64915_CORR_PHONE_MROBB_TMARSHALL.pdf	64,915
1	Regulatory	US	5/19/2006	Book 82	FDA Correspondence - Email	Email - T.Marshall/S.Goldie regarding Pre-NDA CMC meeting. IND Submission S-139 attached.	2006-05-19_64915_CORR_EMAIL_TMARSHALL_SGOLDIE.pdf	64,915
1	Regulatory	US	5/18/2006	Book 82	FDA Submission - IND	IND Safety Report. Initial Written Report. S-140	S-140	64,915
1	Regulatory	US	5/17/2006	Book 82	FDA Correspondence - Email	Email - L.Tanner/M.Robb. To discuss comments and questions (pre-NDA meeting with FDA).	2006-05-17_64915_CORR_EMAIL_MROBB_LTANNER.pdf	64,915
1	Regulatory	US	5/17/2006	Book 82	FDA Submission - IND	Other. Type B Meeting Request: Pre-NDA CMC. S-139	S-139	64,915
1	Regulatory	US	5/8/2006	Book 82	FDA Correspondence - Email	L.Tanner/M.Robb - Response to FDA comment (SN#138) regarding scope and content of NDA.	2006-05-08_64915_CORR_EMAIL_MROBB_LTANNER.pdf	64,915
1	Regulatory	US	5/8/2006	Book 82	FDA Submission - IND	Other: Response to FDA Comments. S-138	S-138	64,915
1	Regulatory	US	5/5/2006	Book 82	FDA Correspondence - Phone	Phone call - L.Tanner/M.Robb to discuss status of written comments to questions in pre-NDA briefing document (IND Serial No.134)	2006-05-05_64915_CORR_PHONE_MROBB_LTANNER.pdf	64,915

1	Regulatory	US	5/5/2006	Book 82	FDA Correspondence - Phone	Phone call - L.Tanner/M.Rabb. Myogen response to Division comments on IND Serial No. 127; date of internal meeting; clarify FDA position on use of audio-visual aids.	2006-05-05_64915_CORR_PHONE_MROBB_LTAN_NER.pdf	64,915
1	Regulatory	US	5/4/2006	Book 97-99	FDA Submission - IND	Information Amendment. Pharmacology/Toxicology. S-137	S-137	64,915
1	Regulatory	US	4/27/2006	Book 82	FDA Submission - IND	Protocol Amendment. New Investigators Update. S-136	S-136	64,915
1	Regulatory	US	4/27/2006	Book 82	FDA Submission - IND	IND Safety Report. Initial Written Report. S-135	S-135	64,915
1	Regulatory	US	4/21/2006	Book 96	FDA Submission - IND	Other: Pre-NDA Briefing Document. S-134	S-134	64,915
1	Regulatory	US	4/21/2006	Book 82	FDA Correspondence - Multiple	Purpose: To test system upgrade and functionality in advance of actual Ambrisentan eCTD.	21_64915_CORR_MULTIPLE_LCURRAN_CDER_ESUB.pdf	64,915
1	Regulatory	US	4/20/2006	Book 82	FDA Correspondence - Letter	The response to the questions regarding the NDA that was submitted in IND Serial No. 127	20_64915_CORR LETTER_NSTOCKBRIDGE_LTANNER.pdf	64,915
1	Regulatory	US	4/19/2006	Book 92-95	FDA Submission - IND	Information Amendment. Pharmacology/Toxicology. S-133	S-133	64,915
1	Regulatory	US	4/19/2006	Book 81	FDA Submission - IND	Other: Population Pharmacokinetic (PK) Data Analysis Plan (DAP) Amendment. S-132	S-132	64,915
1	Regulatory	US	4/17/2006	Book 81	FDA Correspondence - Phone	Phone call L.Tanner/M.Robb regarding status of FDA responses to questions relative to the NDA submitted in S-127	17_64915_CORR_PHONE_MROBB_LTAN_NER.pdf	64,915
1	Regulatory	US	4/11/2006	Book 81	FDA Correspondence - Email	Email with the Word Attachment - L.Tanner/M.Robb regarding status of FDA responses to questions relative to the NDA the NDA submitted in S-127	11_64915_CORR_EMAIL_MROBB_LTAN_NER.pdf	64,915
1	Regulatory	US	4/11/2006	Book 81	FDA Correspondence - Phone	Phone call L.Tanner/M.Robb regarding status of FDA responses to questions relative to the NDA submitted in S-127	11_64915_CORR_PHONE_MROBB_LTAN_NER.pdf	64,915
1	Regulatory	US	4/5/2006	Book 81	FDA Correspondence - Phone	Phone call - L.Tanner/N.Beailey regarding analysis of pharmacokinetic parameters vs. QTc interval assessments.	05_64915_CORR_PHONE_LTANNER_NBE_ASLEY.pdf	64,915

1	Regulatory	US	4/5/2006	Book 91	FDA Submission - IND	Information Amendment. Pharmacology/Toxicology. S-131	S-131	64,915
1	Regulatory	US	3/29/2006	Book 81	FDA Submission - IND	Protocol Amendment. New Investigators and Investigator Update. S-130	S-130	64,915
1	Regulatory	US	3/24/2006	Book 81	FDA Submission - IND	Information Amendment Pharmacology/Toxicology. S-129	S-129	64,915
1	Regulatory	US	3/23/2006	Book 81	FDA Correspondence - Phone	Phone call, L.Tanner/M.Robb - Clarification of FDA participants for pre-NDA meeting scheduled May 19, 2006.	23_64915_CORR_PHONE_MROBB_LTAN NER.pdf	64,915
1	Regulatory	US	3/23/2006	Book 89-90	FDA Submission - IND	Information Amendment. Pharmacology/Toxicology. S-128	S-128	64,915
1	Regulatory	US	3/23/2006	Book 81	FDA Correspondence - Email	E-mail from L.Tanner /M.Robb to obtain feedback from the statisticians on how to address their recommendations regarding the methodology used in the DAPs for the individual Phase 3 studies AMB-320 and AMB-321.	23_64915_CORR_EMAIL_LTANNER_MRO BB.pdf	64,915
1	Regulatory	US	3/21/2006	Book 81	FDA Correspondence - Phone	Phone call, L.Tanner/M.Robb - Clarification of FDA participants for pre-NDA meeting scheduled May 19, 2006.	21_64915_CORR_PHONE_MROBB_LTAN NER.pdf	64,915
1	Regulatory	US	3/20/2006	Book 81	FDA Correspondence - Fax	Fax from M.Robb/L.Tanner regarding Pre-NDA meeting conformation with FDA on May 19, 2006.	20_64915_CORR_FAX_MROBB_LTANNER .pdf	64,915
1	Regulatory	US	3/16/2006	Book 81	FDA Correspondence - Letter	Letter from N.Stockbridge/L.Tanner - Comments (Clinical Pharmacology and Biopharmaceutics) on AMB submission.	16_64915_CORR_LETTER_NSTOCKBRID GE_LTANNER.pdf	64,915
1	Regulatory	US	3/15/2006	Book 81	FDA Submission - IND	Other. Requirements and Format of NDA. S-127	S-127	64,915
1	Regulatory	US	3/14/2006	Book 81	FDA Correspondence - Email	L.Tanner/M.Robb - Email regarding IND 64,915; Serial No. 127; Requirements and Format of NDA.	15_64915_CORR_EMAIL_LTANNER_MRO BB.pdf	64,915
1	Regulatory	US	3/14/2006	Book 81	FDA Correspondence - Letter	Letter from N.Stockbridge/L.Tanner with the comments on AMB submission.	14_64915_CORR_LETTER_NSTOCKBRID GE_LTANNER.pdf	64,915
1	Regulatory	US	3/14/2006	Book 81	FDA Correspondence - Email	L.Curran/K.Edmunds - Email regarding Pilot Submission.	14_64915_CORR_EMAIL_LCURRAN_KED MUNDS.pdf	64,915

1	Regulatory	US	3/10/2006	Book 81	FDA Correspondence - Phone call	L. Tanner/M.Robb phone call regarding feedback on : submission of the rat carcinogenicity, acceptability of cross-reference to NDA in the IND Annual Report, notification of submission with questions on scope, format and date of pre-NDA meeting.	64,915
1	Regulatory	US	3/8/2006	Book 81	FDA Submission - IND	Other: Type B Meeting Request: Pre-NDA. S-126	2006-03-10_63412_CORR_PHONE_LTANNE_R_MROBB_.pdf 64,915
1	Regulatory	US	3/2/2006	Book 81	FDA Submission - IND	Protocol Amendment: New Investigators and 1572 Update. S-125	64,915
1	Regulatory	US	3/2/2006	Book 81	FDA Submission - IND	IND Safety Report. Follow-up to a Fax Report: S2597. S-124	64,915
1	Regulatory	US	2/27/2006	Book 81	FDA Correspondence - Phone call/Fax	L. Curran called M.Robb to inform her that he would be faxing a 7-Day Safety Report. Fax 7-Day Safety Report.	2006-02-27_64915_CORR_PHONE_FAX_LC_URRAN_MROBB_.pdf 64,915
1	Regulatory	US	2/21/2006	Book 81	FDA Submission - IND	Other: Response to the IND correspondence. S-123	S-123 64,915
1	Regulatory	US	2/15/2006	Book 81	FDA Correspondence - Letter	Letter from N.Stockbridge to L. Tanner regarding FDA approval for fast track designation.	2006-02-15_64915_CORR LETTER_NSTOC_KBRIDGE_LTANNER_.pdf 64,915
1	Regulatory	US	2/9/2006	Book 88	FDA Submission - IND	Other: Request for Fast Track Designation. S-122	S-122 64,915
1	Regulatory	US	2/8/2006	Book 81	FDA Correspondence - Letter	Letter from N.Stockbridge to L. Tanner regarding Myogen request for additional clarification to a letter dated 22 December 2005 regarding the changes to the statistical analysis plans that was reflected in the protocol amendments to AMB-320 and AMB-321.	2006-02-08_64915_CORR LETTER_NSTOC_KBRIDGE_LTANNER_.pdf 64,915
1	Regulatory	US	2/8/2006	Book 81	FDA Correspondence - Phone call	Phone call L. Tanner/M.Robb. Confirm whether the popPK DAP has been reviewed and whether Division comments will be forthcoming.	2006-02-08_63412_CORR_PHONE_LTANNE_R_MROBB_.pdf 64,915
1	Regulatory	US	1/30/2006	Book 81	FDA Correspondence - Phone call	Phone call - L. Tanner/B.N.Breasley regarding status of Clinical QT/QTC Study AMB-104	2006-01-30_64915_CORR_PHONE_LTANNE_R_BNBEASLEY_.pdf 64,915

1	Regulatory	US	1/27/2006	Book 81	FDA Submission - IND	IND Safety Report. Initial Written Report: 51629. Follow-Up to a Written Report: 52559. S-121	S-121	64,915
1	Regulatory	US	1/26/2006	Book 87	FDA Submission - IND	Protocol Amendment. Change in Protocol AMB-104. S-120	S-120	64,915
1	Regulatory	US	1/25/2006	Book 81	FDA Submission - IND	Protocol Amendment. New investigators and 1572 Update. S-119	S-119	64,915
1	Regulatory	US	1/24/2006	Book 86	FDA Submission - IND	Protocol Amendment. Change in Protocol AMB-222. S-118	S-118	64,915
1	Regulatory	US	1/23/2006	Book 81	FDA Correspondence - Phone call	Phone call L. Tanner/M. Robb. Feedback on submitting additional documentation to support changes in the revised Protocol AMB-222 that was submitted in Serial No. 115	2006-01-23_64915_CORR_PHONE_LTANNE_R_MROBB.pdf	64,915
1	Regulatory	US	1/23/2006	Book 85	FDA Submission - IND	Protocol Amendment. Change in Protocol AMB-107. S-117	S-117	64,915
1	Regulatory	US	1/19/2006	Book 81	FDA Correspondence - Phone call	Phone call - L. Tanner/L. Velazquez regarding feedback on Bioequivalence Protocol AMB-103 submitted on 12/19/2005 S-108.	19_64915_CORR_PHONE_LTANNE_R_LVELAZQUEZ.pdf	64,915
1	Regulatory	US	1/16/2006	Book 81	FDA Submission - IND	IND Safety Report. Follow-up to a written Report: 52566. S-116	S-116	64,915
1	Regulatory	US	1/13/2006	Book 84	FDA Submission - IND	Protocol Amendment. Change in Protocol. S-115	S-115	64,915
1	Regulatory	US	1/10/2006	Book 81	FDA Correspondence - Phone call	Phone call L. Tanner/M. Robb. Follow-up on clarification on FDA statistical comments to protocol amendments for AMB-320 and AMB-321.	2006-01-10_64915_CORR_PHONE_LTANNE_R_MROBB.pdf	64,915
1	Regulatory	US	1/9/2006	Book 81	FDA Submission - IND	IND Safety Report. Follow-up to a written Report: 51627. S-114	S-114	64,915
1	Regulatory	US	1/5/2006	Book 81	FDA Correspondence - Email	Email - M. Robb/L. Tanner regarding IND 64,915 Letairis trade name - Response to Questions.	2006-01-05_64915_CORR_EMAIL_LTANNE_R_MROBB.pdf	64,915
1	Regulatory	US	1/4/2006	Book 81	FDA Submission - IND	IND Safety Report. Initial Written Report. S-113	S-113	64,915

1	Regulatory	US	12/20/05	Book 51	FDA Correspondence - Email	Email - M.Robb/L.Tanner Chairperson on Statistical Committee SINA and S.C.E.S. INDication	2005-01- R_MROBB.pdf
1	Regulatory	US	12/28/2005	Book 52	FDA Correspondence - Fax	Email - M.Robb/L.Tanner regarding IND 64,915 Letairis trade name.	2005-12- 28_64915_CORR_EMAIL_LTANNER_R_MROBB.pdf
1	Regulatory	US	12/27/2005	Book 52	FDA Correspondence - Fax	The FDA minutes for the Type C meeting scheduled as a teleconference on 15 December 2005 to discuss the PK/PD development plan. Attached are Internal (Myogen) Minutes for the same meeting.	2005-12- 27_64915_CORR_FAX_MTG_MINUTES_LTANNER_MROBB.pdf
1	Regulatory	US	12/22/2005	Book 52	FDA Correspondence - Letter	Letter from N. Stockbridge to L. Tanner regarding comments on ARIES-2 DAP.	2005-12- 22_64915_CORR LETTER_NSTOC_KBRIDGE_LTANNER.pdf
1	Regulatory	US	12/21/2005	Book 52	FDA Correspondence - Phone call	Phone call on 12-20-2005 and 12-21- 2005 L.Tanner/M.Robb. Intent to submit application for fast track designation.	2005-12- 21_64915_CORR_PHONE_LTANNER_R_MROBB.pdf
1	Regulatory	US	12/21/2005	Book 52	FDA Submission - IND	IND Safety Report. Initial Written Report: 51627. S-112	2005-12- S-112
1	Regulatory	US	12/21/2005	Book 52	FDA Submission - IND	IND Safety Report. Initial Written Report: 52559. S-111	2005-12- S-111
1	Regulatory	US	12/20/2005	Book 80	FDA Submission - IND	Protocol Amendment. New Protocol (AMB-107) and New Investigator. S 110	2005-12- S-110
1	Regulatory	US	12/19/2005	Book 52	FDA Correspondence - Email	ECG measurements on Baseline and Treatment Days in Protocol AMB- 104.	2005-12- 19_64915_CORR_EMAIL_LTANNER_R_MROBB.pdf
1	Regulatory	US	12/19/2005	Book 52	FDA Submission - IND	IND Safety Report. Initial Written Report: 52555. S-109	2005-12- S-109
1	Regulatory	US	12/19/2005	Book 79	FDA Submission - IND	Protocol Amendment. New Protocol (AMB-103) and New Investigators. S-108	2005-12- S-108
1	Regulatory	US	12/19/2005	Book 52	FDA Correspondence - Phone call	Phone call. T.Marshall/M.Robb. Feedback from Ambisentan Chemistry Reviewer for Drug Substance and Drug Product IND Amendments.	2005-12- 19_64915_CORR_PHONE_TMARSH_ALL_MROBB.pdf
1	Regulatory	US	12/16/2005	Book 52	FDA Correspondence - Phone call	Phone call. T.Marshall/M.Robb. Request Feedback from Ambisentan Chemistry Reviewer for Drug Product Update.	2005-12- 16_64915_CORR_PHONE_TMARSH_ALL_MROBB.pdf

1	Regulatory	US	12/15/2005	Book 52	FDA Correspondence - Email	Email - L.Tanner/M.Robb. Subject: List of Myogen Participants Type C Meeting 12/15/2005.	2005-12- R_MROBB_1.pdf	64,915
1	Regulatory	US	12/15/2005	Book 52	FDA Correspondence - Email	Email - L.Tanner/M.Robb. Subject: Clarification on Medical Review Comments QT/QTC Protocol AMB-104.	2005-12- R_MROBB.pdf	64,915
1	Regulatory	US	12/14/2005	Book 52	FDA Correspondence - Email	Email - L.Tanner/M.Robb. Subject: Slides Top Line Results Phase 3 Study AMB-321; IND 64,915 Ambrisentan.	2005-12- R_MROBB.pdf	64,915
1	Regulatory	US	12/14/2005	Book 52	FDA Correspondence - Phone call	Phone call from L. Tanner to M. Robb. Subject: Type C teleconference meeting scheduled 12/15/05; QT/QTC Study (AMB-104)	2005-12- R_MROBB.pdf	64,915
1	Regulatory	US	12/13/2005	Book 52	FDA Correspondence - Email	Email - L.Tanner/M.Robb. Conformation of FDA Participants Teleconference - 12/15/2005.	2005-12- R_MROBB.pdf	64,915
1	Regulatory	US	12/12/2005	Book 52	FDA Correspondence - Phone call	Phone call (on 12/09/05 and 12/12/05) from L. Tanner to M. Robb. Subject: Clarify FDA participations Type C teleconference meeting scheduled 12/15/2005.	2005-12- R_MROBB.pdf	64,915
1	Regulatory	US	12/6/2005	Book 52	FDA Correspondence - Email	Email - L.Tanner/M.Robb. Subject: Myogen Participants and Teleconference Instruction.	2005-12- R_MROBB.pdf	64,915
1	Regulatory	US	12/1/2005	Book 52	FDA Correspondence - Email	Email - L.Tanner/M.Robb. Subject: Electronic Copy of S-106 - Analysis Plan for Population Pharmacokinetic Modeling.	2005-12- R_MROBB.pdf	64,915
1	Regulatory	US	12/1/2005	Book 73-78	FDA Submission - IND	Information Amendment. Clinical Study Report EE002. S-107	S-107	64,915
1	Regulatory	US	12/1/2005	Book 52	FDA Correspondence - Phone call	Phone call - L.Tanner/M.Robb. Purpose: To confirm receipt of desk copies of PK/PD briefing package for the teleconference meeting scheduled 15 December 2005 and update on IND submissions this week.	2005-12- R_MROBB.pdf	64,915
1	Regulatory	US	11/30/2005	Book 52	FDA Submission - IND	Other: Data Analysis Plan for Population Pharmacokinetic Modeling. S-106	S-106	64,915

1	Regulatory	US	11/30/2005	Book 72	FDA Submission - IND	Other: Briefing Document for Type c.Meeting. S-105	64,915
1	Regulatory	US	11/30/2005	Book 71	FDA Submission - IND	Protocol. New Protocol and New Investigator. S-104	64,915
1	Regulatory	US	11/30/2005	Book 70	FDA Submission - IND	Other: Data Analysis Plans. S-103	64,915
1	Regulatory	US	11/29/2005	Book 69	FDA Submission - IND	Other: Data Analysis Plans. S-102	64,915
1	Regulatory	US	11/29/2005	Book 65-68	FDA Submission - IND	Information Amendment. Pharmacology/Toxicology. S-101	64,915
1	Regulatory	US	11/28/2005	Book 52	FDA Correspondence - Phone call	Phone call - L.Tanner/M.Robb. Myogen response to FDA comments on the QT/QTC study design (Serial No. 096)	2005-11-28_64915_CORR_PHONE_LTANNE_R_MROBB.pdf
1	Regulatory	US	11/28/2005	Book 64	FDA Submission - IND	Other. Data Analysis Plan. S-100	64,915
1	Regulatory	US	11/23/2005	Book 63	FDA Submission - IND	Protocol Amendment. New Investigators. S-099	64,915
1	Regulatory	US	11/16/2005	Book 52	FDA Correspondence - Phone call	Phone call - L.Tanner/M.Robb. Purpose: Instruction for shipping PK/PD package for the teleconference meeting scheduled 12/15/2005.	2005-11-16_64915_CORR_PHONE_LTANNE_R_MROBB.pdf
1	Regulatory	US	11/14/2005	Book 52	FDA Correspondence - Phone call	Phone call - L.Tanner/M.Robb. Purpose: To confirm timing of submitting the PK/PD briefing package for the teleconference meeting scheduled 15 December 2005.	2005-11-14_64915_CORR_PHONE_LTANNE_R_MROBB.pdf
1	Regulatory	US	11/11/2005	Book 62	FDA Submission - IND	Protocol Amendment. Change in Protocol. Information Amendment Clinical. S-098	64,915
1	Regulatory	US	11/11/2005	Book 52	FDA Submission - IND	Information Amendment. Pharmacology/Toxicology 2-Year Rat and Mouse Carcinogenicity Studies. S-097	64,915
1	Regulatory	US	11/10/2005	Book 52	FDA Correspondence - Phone call	Phone call - L.Tanner/W.Link on 11/10/05 and 11/09/05 regarding 2 year carcinogenicity (CAC) studies in mice and rats.	2005-11-10_64915_CORR_PHONE_LTANNE_R_WLINK.pdf

1	Regulatory	US	11/9/2005	Book 52	FDA Correspondence - Phone call	Phone call - L.Tanner/M.Robb on 11/08/05 and 11/09/05 regarding 2 year carcinogenicity (CAC) studies in mice and rats. Arrange teleconference with Dr. William Link to provide survival update on CAC studies.	2005-11-09_64915_CORR_PHONE_LTANNER_MROBB.pdf	64,915
1	Regulatory	US	11/7/2005	Book 52	FDA Submission - IND	Other: Response to FDA Comments on QT/QTc Study Design. S-096	S-096	64,915
1	Regulatory	US	11/4/2005	Book 61	FDA Submission - IND	Protocol. New Protocol and New Investigator. S-095	S-095	64,915
1	Regulatory	US	11/4/2005	Book 52	FDA Submission - IND	Other: Trademark Evaluation. S-094	S-094	64,915
1	Regulatory	US	10/24/2005	Book 52	FDA Correspondence - Email	Email from R. Fortney to L. Weissberger regarding minutes from October 19, 2005 teleconference.	2005-10-24_64915_CORR_EMAIL_RFORTNEY_LWEISSBERGER.pdf	64,915
1	Regulatory	US	10/21/2005	Book 60	FDA Submission - IND	Protocol Amendment: New Investigators. Other: Revisions to FDA Forms 1572. S-093	S-093	64,915
1	Regulatory	US	10/20/2005	Book 52	FDA Correspondence - Phone call	Phone call from L. Weissberger to M. Robb. Subject: QT/QTc study - comments on study design submitted for both darusentan (Serial No. 076) and ambrisentan (Serial No. 086)	2005-10-20_64915_CORR_PHONE_LWEISSBEGER_MROBB.pdf	64,915
1	Regulatory	US	10/19/2005	Book 52	FDA Correspondence - Letter	Letter from R. Fortney to L. Weissberger. Teleconference Minutes from FDA and Internal Minutes - October 19, 2005.	2005-10-19_64915_CORR_LETTER_RFORTNEY_LWEISSBERGER.pdf	64,915
1	Regulatory	US	10/19/2005	Book 52	FDA Correspondence - Email	Email from L. Tanner to R. Fortney regarding teleconference on October 19, 2005.	2005-10-19_64915_CORR_EMAIL_RFORTNEY_LTANNER.pdf	64,915
1	Regulatory	US	10/18/2005	Book 52	FDA Submission - IND	Protocol. New Protocol and New Investigator. S-092	S-092	64,915
1	Regulatory	US	10/13/2005	Book 52	FDA Correspondence - Email	Email from R. Fortney to L. Weissberger regarding FDA letter with comments on QT/QTc Study.	2005-10-13_64915_CORR_EMAIL_RFORTNEY_LWEISSBERGER.pdf	64,915
1	Regulatory	US	10/12/2005	Book 52	FDA Correspondence - Letter	Letter from N. Stockbridge to L. Weissberger. Comments on QT/QTc study proposal for Ambrisentan.	2005-10-12_64915_CORR_LETTER_NSTOCKBRIDGE_LWEISSBERGER.pdf	64,915

1	Regulatory	US	10/12/2005	Book 52	FDA Correspondence - Phone call	Phone call, L. Tanner/R. Fortney. Subject: Teleconference DAP; S-084	2005-10- 12_64915_CORR_PHONE_LTANNE_R_RFORTNEY.pdf	64,915
1	Regulatory	US	10/12/2005	Book 52	FDA Correspondence - Email	Email from L. Tanner to R. Fortney regarding Teleconference on 10/19/2005, additional participant.	2005-10- 12_64915_CORR_EMAIL_RFORTNEY_LTANNER.pdf	64,915
1	Regulatory	US	10/11/2005	Book 52	FDA Correspondence - Phone call	Phone call, L. Tanner/R. Fortney. L. Tanner called R. Fortney on 10/06/05, 10/10/05 and 10/11/05. Subject: Teleconference DAP; S-084	2005-10- 11_64915_CORR_PHONE_LTANNE_R_RFORTNEY.pdf	64,915
1	Regulatory	US	10/11/2005	Book 52	FDA Correspondence - Email	Email from R. Fortney to L. Weissberger regarding QT Study Comments.	2005-10- 11_64915_CORR_EMAIL_RFORTNEY_LTANNER_R_RFORTNEY.pdf	64,915
1	Regulatory	US	10/5/2005	Book 52	FDA Correspondence - Phone call	Phone call, L. Tanner/R. Fortney. Subject: Reschedule Type C Meeting; S-087	2005-10- 05_64915_CORR_PHONE_LTANNE_R_RFORTNEY.pdf	64,915
1	Regulatory	US	10/4/2005	Book 59	FDA Submission - IND	Information Amendment. Chemistry, Manufacturing, and Controls. S-091	2005-10- S-091	64,915
1	Regulatory	US	10/4/2005	Book 52	FDA Submission - IND	IND Safety Report: Follow-up to a Written Report. S-090	S-090	64,915
1	Regulatory	US	10/4/2005	Book 52	FDA Correspondence - Phone call	Phone call, L. Tanner/R. Fortney. Subject: Intention to Cancel or Reschedule Type C Meeting; Serial No. 087	2005-10- 04_64915_CORR_PHONE_LTANNE_R_RFORTNEY.pdf	64,915
1	Regulatory	US	9/28/2005	Book 52	FDA Correspondence - Letter	Letter from N. Stockbridge to L. Tanner regarding FDA Division comments on the Data Analysis Plan for AMB-321.	2005-09- 28_64915_CORR LETTER_NSTOCKBRIDGE_LTANNER.pdf	64,915
1	Regulatory	US	9/26/2005	Book 58	FDA Submission - IND	Protocol Amendment: New Investigators: Gabbay, Channick, Frost, Waxman, Sulica, Taichman, Olschewski, Souza, Pulido, Rivera, Swisher, Booth, Ross, White. S-089	S-089	64,915
1	Regulatory	US	9/21/2005	Book 52	FDA Correspondence - Fax	Fax from M. Robb to L. Tanner. Subject: Conformation of 11/08/2005 Teleconference.	2005-09- 21_64915_CORR_FAX_MROBB_LTANNER.pdf	64,915

1	Regulatory	US	9/20/2005	Book 52	FDA Correspondence - Phone call	Phone call L. Tanner/M. Robb. Finalize Date/Time of Type C Teleconference/Meeting. (Serial No. 087); Status of DAP (Serial No. 084)	20_64915_CORR_PHONE_LTANNE_R_ROBBM.pdf	2005-09-	64,915
1	Regulatory	US	9/19/2005	Book 52	FDA Correspondence - Phone call	Phone call T. Marshall/M. Robb. Subject: Follow-up to determine if Chemistry reviewer has any concerns regarding the drug substance IND update. IND 64,915, Serial No. 083, 4 Aug 05.	19_64915_CORR_PHONE_TMARSH_ALL_MROBB.pdf	2005-09-	64,915
1	Regulatory	US	9/19/2005	Book 52	FDA Correspondence - Phone call	Phone call L. Tanner/M. Robb. Finalize Date/Time of Type C Teleconference/Meeting. (Serial No. 087); Status of DAP (Serial No. 084)	19_64915_CORR_PHONE_LTANNE_R_ROBBM.pdf	2005-09-	64,915
1	Regulatory	US	9/15/2005	Book 52	FDA Correspondence - Letter	Letter from N. Stockbridge to L. Tanner. Conformation that Food Effect Study Does not Need to be Repeated	15_64915_CORR LETTER_NSTOC_KBRIDGE_LTANNER.pdf	2005-09-	64,915
1	Regulatory	US	9/15/2005	Book 52	FDA Submission - IND	Information Amendment. Pharmacology/Toxicology 2-year Rat and Mouse Carcinogenicity Studies. S-088	S-088		64,915
1	Regulatory	US	9/15/2005	Book 52	FDA Correspondence - Phone call	Phone called (1:30 p.m.) from L. Tanner to M. Robb regarding proposed Date for Type C Meeting PK/PD.	15_64915_CORR_PHONE_LTANNE_R_ROBBM.pdf	2005-09-	64,915
1	Regulatory	US	9/15/2005	Book 52	FDA Correspondence - Phone call	Phone called (10:00 a.m.) from M. Robb to L. Tanner regarding proposed Date for Type C Meeting PK/PD.	15_64915_CORR_PHONE_LTANNE_R_ROBBM_2.pdf	2005-09-	64,915
1	Regulatory	US	9/12/2005	Book 52	FDA Correspondence - Email	Email from L. Tanner to M. Robb regarding a Type C Meeting Request. S-087. Submission included.	12_64915_CORR_EMAIL_LTANNE_R_MROBB.pdf	2005-09-	64,915
1	Regulatory	US	9/12/2005	Book 52	FDA Submission - IND	Other: Type C Meeting Request, Development Plan for Biopharmaceutics and Clinical Pharmacology. S-087	S-087		64,915
1	Regulatory	US	9/7/2005	Book 52	FDA Submission - IND	Other: Request for FDA Review of QT/QTc Study Proposal. S-086	S-086		64,915

1	Regulatory	US	9/7/2005	Book 52	FDA Correspondence - Phone call	Phone call. L. Tanner/M. Robb. Subject: request to Submit QT/QTC Study Proposal to IND.	2005-09- 07_64915_CORR_PHONE_MROBB_- LTANNER.pdf	64,915
1	Regulatory	US	8/31/2005	Book 52	FDA Correspondence - Email	Email from L. Weissberger to M. Robb regarding a summary of the QT/QTC evaluation proposing for Ambisentan (64,915) and Darusentan (59,669).	2005-08- 31_64915_CORR_EMAIL_WEISSBE RGERL_ROBBM.pdf	64,915
1	Regulatory	US	8/25/2005	Book 52	FDA Submission - IND	IND Safety Reports. S-085	S-085	64,915
1	Regulatory	US	8/24/2005	Book 52	FDA Correspondence - Phone call	Phone call. M. Robb/L. Tanner. Subject: FDA Decision that Food Effect Study Does not Need to Be Repeated	2005-08- 24_64915_CORR_PHONE_MROBB_- LTANNER.pdf	64,915
1	Regulatory	US	8/23/2005	Book 52	FDA Correspondence - Phone call	Phone call from M. Robb to L. Tanner. Subject: Clarify 7-day SAE Process for IND 63,412; Confirm FDA receipt of PDF file for Serial No. 084 (IND 64,915); Status of Serial No. 082 Food Effect (64,915); Potential meeting PK/PD development plan (IND 64,915)	2005-08- 23_64915_CORR_PHONE_MROBB_- LTANNER.pdf	64,915
1	Regulatory	US	8/22/2005	Book 52	FDA Submission - IND	Other: Data Analysis Plan (AMB-321) for FDA Feedback. S-084	S-084	64,915
1	Regulatory	US	8/22/2005	Book 52	FDA Correspondence - Phone call	Phone call from L. Tanner to M. Robb. Subject: Clarify 7-day SAE Process; Status of Serial No. 082 Food Effect; Notification of DAP Submission.	2005-08- 22_64915_CORR_PHONE_LTANNE R_MROBB.pdf	64,915
1	Regulatory	US	8/22/2005	Book 52	FDA Correspondence - Fax	Fax from L. Tanner to M. Robb. Subject: 7 Day Safety Report - Initial Manufacturer's Report No. 52505.	2005-08- 22_64915_CORR_FAX_LTANNER_- MROBB.pdf	64,915
1	Regulatory	US	8/19/2005	Book 52	FDA Correspondence - Phone call	Phone call. From M. Cooper to T. Marshall. Subject: Division feedback on ambisentan starting materials (IND 64,915, Serial No. 083)	2005-08- 19_64915_CORR_PHONE_MCOOP ER_TMARSHALL.pdf	64,915
1	Regulatory	US	8/19/2005	Book 52	FDA Correspondence - Phone call	Phone call. From T. Marshall to M. Robb. On 8/18/2005 T. Marshall left voice message and on 8/19/2005 phoned M. Robb. Subject: Follow-up on requested feedback on starting materials from IND 64,915, Serial No. 083 dated 08/04/2005.	2005-08- 19_64915_CORR_PHONE_TMARSH ALL_MROBB.pdf	64,915

1	Regulatory	US	8/4/2005	Book 57	FDA Submission - IND	Information Amendment: Chemistry, Manufacturing and Controls. S-083	S-083	64,915
1	Regulatory	US	8/4/2005	Book 52	FDA Correspondence - Phone call	Phone call from L. Tanner to M. Robb. Subject: Confirm submission of S-082 Formulations Food/Effect.	2005-08- 04_64915_CORR_PHONE_LTANNE_R_MROBB.pdf	64,915
1	Regulatory	US	8/4/2005	Book 52	FDA Correspondence - Phone call	Phone call from T. Marshall to M. Robb. Left phone message. Subject: Informed Project Manager of Drug Substance CMC Information Amendment and Requested Feedback on Starting Materials.	2005-08- 04_64915_CORR_PHONE_TMARSH_ALL_MROBB.pdf	64,915
1	Regulatory	US	8/4/2005	Book 52	FDA Correspondence - Email	Email from L. Tanner to M. Robb regarding submission S-082. Submission included.	2005-08- 04_64915_CORR_EMAIL_LTANNE_R_MROBB.pdf	64,915
1	Regulatory	US	8/3/2005	Book 52	FDA Submission - IND	Response To FDA Request For Information. S-082	S-082	64,915
1	Regulatory	US	7/26/2005	Book 56	FDA Submission - IND	Protocol Amendment. New Investigators.S-081 Keogh, Noordgraaf, Jennings, Murali, Schilz, Campos, Chalkin, Arakaki, Cardozo, Meyer, Kopisa, Hassoun, Feldman. S-081	S-081	64,915
1	Regulatory	US	6/30/2005	Book 51	FDA Submission - IND	Protocol Amendment. Annual Report. S-080	S-080	64,915
1	Regulatory	US	6/20/2005	Book 51	FDA Submission - IND	Protocol Amendment: New Investigators. Badesch, Foley, McGoon, Hassoun, Oudiz. Other: Revisions to FDA Form 1572. S-079	S-079	64,915
1	Regulatory	US	5/24/2005	Book 51	FDA Submission - IND	General Correspondence: Converting ARIES-2 Study Sites to ARIES-1. S-078	S-078	64,915
1	Regulatory	US	5/23/2005	Book 51	FDA Submission - IND	Protocol Amendment: New Investigators. Baratz, Barst, Fairman, Garcia, Mandel, Oudiz, Test. S-077	S-077	64,915
1	Regulatory	US	5/6/2005	Book 51	FDA Correspondence - Phone call	Phone call. L.Weissberger/M.Robb. Subject: Follow-up on requirement for food effects study.	2005-05- 06_64915_CORR_PHONE_LWEISS_BERGER_MROBB.pdf	64,915

1	Regulatory	US	5/3/2005	Book 51	FDA Correspondence - Phone call	Phone call. L.Weissberger/M.Robb. Subject: Clarify message from Dr. Velazquez.	2005-05-	64,915
1	Regulatory	US	5/2/2005	Book 51	FDA Correspondence - Phone call	Phone call. L.Weissberger/L.Velazquez. Subject: Protocol AMB-222.	02_64915_CORR_PHONE_LWEISS BERGER_LVELAZQUEZ.pdf	64,915
1	Regulatory	US	4/29/2005	Book 51	FDA Correspondence - Email	Email/M.Robb/L.Weissberger - 2- Year Rat and Mouse Bioassays.	2005-04-	64,915
1	Regulatory	US	4/27/2005	Book 51	FDA Submission - IND	Protocol Amendment: New Investigators. S-076 Kilingер, Hurewitz, Feldman, Arfaei, Nikolaevich. S-076	29_64915_CORR_EMAIL_LTANNE R_MROBB.pdf	64,915
1	Regulatory	US	4/25/2005	Book 51	FDA Correspondence - Phone call	Phone call. L.Weissberger/T.Link. FDA Response to our proposal for carcinogenicity studies.	2005-04-	64,915
1	Regulatory	US	4/22/2005	Book 51	FDA Correspondence - Phone call	Call to discuss 2-yr. Carcinogenicity studies.	25_64915_CORR_PHONE_LWEISS BERGER_WLINK.pdf	64,915
1	Regulatory	US	4/12/2005	Book 51	FDA Submission - IND	Protocol Amendment: Change in Protocol. S-075	2005-04-	64,915
1	Regulatory	US	4/5/2005	Book 53-55	FDA Submission - IND	Vol. 1 - 3 -Response to FDA Request for Information. S-074	22_64915_CORR_PHONE_LWEISS	64,915
1	Regulatory	US	4/1/2005	Book 51	FDA Correspondence - Email	Email/M.Robb/L.Weissberger - Response to FDA Request for Information	S-074	64,915
1	Regulatory	US	3/31/2005	Book 50	FDA Submission - IND	Protocol Amendment - L. Weissberger. New Investigator, Test, Noordgraaf, Kovalenko, Zagolin, Revisions to FDA Forms 1572. S-073	01_64915_CORR_EMAIL_LTANNE R_MROBB.pdf	64,915
1	Regulatory	US	3/28/2005	Book 50	FDA Correspondence - Fax	Response to a request from FDA, and follow-up	2005-03-	64,915
1	Regulatory	US	3/24/2005	Book 50	FDA Submission - IND	Follow-up to a written Report. S- 072	28_64915_CORR_FAX_JFLIARD_N BEASLEY.pdf	64,915
1	Regulatory	US	3/16/2005	Book 50	FDA Correspondence - Letter	Stockbridge, N., Letter: Response to S- 068 - Protocol Submission	2005-03-	64,915
1	Regulatory	US					16_64915_CORR LETTER_MROBB _LWEISSBERGER.pdf	

1	Regulatory	US	3/9/2005	Book 50	FDA Submission - IND	L.Weissberger. Information Amendment. Pharmacology/Toxicology 2 year Rat and Mouse Carcinogenicity Studies. S-071	64,915
1	Regulatory	US	3/4/2005	Book 50	FDA Submission - IND	L. Weissberger. Protocol Amendment: New Investigators, Hassoun, Tereshchenko, Chakinala. S-070	64,915
1	Regulatory	US	2/18/2005	Book 50	FDA Submission - IND	L. Weissberger. General Correspondence. S-069	64,915
1	Regulatory	US	2/16/2005	Book 50	FDA Correspondence - Phone call	FDA Contact Report - Telephone. M.Robb/L.Weissberger. Subject: Existing "Food Effect" Study. 16_64915_CORR_PHONE_LWEISS BERGER_MROBB.pdf	64,915
1	Regulatory	US	2/15/2005	Book 50	FDA Submission - IND	L.Weissberger. New Protocol: AMB-222. S-068	64,915
1	Regulatory	US	2/4/2005	Book 50	FDA Submission - IND	L.Weissberger. Protocol Amendment New Investigators, Colque, Noordgraaf, Chazova (AMB-321, AMB-320/321-E) S-067	64,915
1	Regulatory	US			FDA Submission - IND	L. Weissberger. Protocol Amendment: New Investigators (AMB-321, AMB-320/321-E) S-066	64,915
1	Regulatory	US			FDA Submission - IND	L. Weissberger. Protocol Amendment: New Investigators (AMB-321, AMB-320/321-E) S-065	64,915
1	Regulatory	US	12/22/2004	Book 50	FDA Submission - IND	FDA Correspondence - Phone call	FDA Contact Report - Telephone. L.Weissberger/W.Link. Subject: Executive CAC decision about lowering dose(s) for 2 year rat and mouse bioassays.
1	Regulatory	US	12/17/2004	Book 50	FDA Submission - IND	17_64915_CORR_PHONE_LINK.pdf	2004-12-17_64915_CORR_PHONE_LINK.pdf
1	Regulatory	US	12/7/2004	Book 50	FDA Submission - IND	L.Weissberger-Information Amendment- Pharmacology/Toxicology. 2-year Rat and Mouse Carcinogenicity. S-064	64,915

1	Regulatory	US	11/12/2004	Book 50	FDA Submission - IND	L. Weissberger - Protocol Amendment: New Investigators: Kramer, M.R., Barst, R.J., Lawrence, E.C., Park, M.H., Schilz, R.J. (AMB-321, AMB-320/321-E) S- 063	64,915
1	Regulatory	US	10/29/2004	Book 49	FDA Submission - IND	L. Weissberger - Protocol Amendment: New Investigators: Langleben, D., Carlson, R., Diez, F., Porcile, R., Ubaldini, J.E., Vico, M.L., Tereschenko, S., Semernin, E.N. (AMB-320, AMB- 321, AMB-320/321-E) S-062	64,915
1	Regulatory	US	10/26/2004	Book 49	FDA Correspondence - Fax	FDA Correspondence - Fax - Meeting Minutes 10/13/04.	2004-10- 26_64915_CORR_FAX_MTG_MINS _2004-10-13.pdf
1	Regulatory	US	10/22/2004	Book 49	FDA Submission - IND	L. Weissberger - Protocol Amendment-New Principal Investigators: Martinez, J.G., Vazquea, J., Chazova, Irina, Y., Kostenko, M.A., Czuriga, I., Landzberg, M.J. (AMB-320, AMB- 321, AMB-320/321-E) S-061	64,915
1	Regulatory	US	10/5/2004	Book 49	FDA Submission - IND	L. Weissberger - Protocol Amendment. New Investigators. M. Amuchastegui, G. Bortman, E. Perna, K. Karloca, O. Abrahamovych, G. Dzyak, N. Kopitsa, V. Kovalenko, S. Polyvoda, F. Kleber, P. Podolec, A. Torbicki, V. McLaughlin, A. Towlar (AMB- 320, AMB-321, AMB-320/321-E) S- 060	64,915
1	Regulatory	US	9/27/2004	Book 49	FDA Submission - IND	Lynn Weissberger - Type C Meeting Information Package. S-059	64,915

1	Regulatory	US	9/7/2004	Book 48	FDA Submission - IND	Lynne Weissberger - Protocol Amendment. New Investigators. R. Sulica, I. Czuriga, P. Podolec, A. Torbicki, I. Ben-Dov, R.P. Allen, R.J. Oudiz (AMB-320, AMB-321, AMB-320/321-E) S-058	S-058	64,915
1	Regulatory	US	8/31/2004	Book 48	FDA Submission - IND	Lynne Weissberger - Annual Report 07-03-2003 through 07-02-2004. S-057	S-057	64,915
1	Regulatory	US	8/27/2004	Book 48	FDA Submission - IND	Protocol Amendment - L. Weissberger - Initial Written Report. 15-Day Safety Alert Report. (AMB-320/321-E) S-056	S-056	64,915
1	Regulatory	US	8/11/2004	Book 48	FDA Correspondence - Fax	Fax from R. Fortney to L. Weissberger. Subject: Meeting confirmation with FDA for October 13, 2004.	2004-08-11_64915_CORR_FAX_RFORTNEY_LWEISSBERGER.pdf	64,915
1	Regulatory	US	8/10/2004	Book 48	FDA Submission - IND	L. Weissberger-Protocol Amendment New Investigators. R. Barst, M. Lamdzberg, M.A.G.Sanchez, J.A. Barbera, D. Badescu, R. Foley (AMB-320, AMB-320/321-E) S-055	S-055	64,915
1	Regulatory	US	8/9/2004	Book 48	FDA Submission - IND	L. Weissberger - Type C Meeting Request to discuss proposed changes to the ambrisentan program. S-054	S-054	64,915
1	Regulatory	US	7/20/2004	Book 48	FDA Correspondence - Phone call	FDA Contact Report - Call to Alisea Sermon. Subject: Schedule Type C Meeting.	20_64915_CORR_PHONE_LWEISSBERGER_ASERMON.pdf	64,915
1	Regulatory	US	7/21/2004	Book 48	FDA Correspondence - Email	FDA Contact Report - Email to A. Sermon. Subject: Meeting Request with the Division of Cardio-Renal drug Products.	21_64915_CORR_EMAIL_LWEISSBERGER_ASERMON.pdf	64,915
1	Regulatory	US	7/16/2004	Book 47	FDA Correspondence - Phone call	FDA Contact Report - Call to M. Robb. Subject: Type C Meeting Request.	16_64915_CORR_PHONE_LWEISSBERGER_MROBB.pdf	64,915

1	Regulatory	US	7/15/2004	Book 47	FDA Correspondence - Email	FDA Contact Report - Email to M. Robb. Subject: Ambrisentan, Type C Meeting Request.	64,915
1	Regulatory	US	7/14/2004	Book 47	FDA Submission - IND	L. Weissberger- Protocol Amendment- New Investigators- A. Frost, P. Galvez, H. Donoso, M. Delcroix, G. Simonneau, J. Behr, R. Fairman, A. Frost (AMB-320, AMB-321, AMB-320/321-E) S-053	64,915
1	Regulatory	US	7/7/2004	Book 47	FDA Submission - IND	L. Weissberger- Protocol Amendment- New Investigators- D. Baratz, J. Edelman, N. Hill, I. Robbins, M. Robbins, S. Shapiro, S. Bhorade (AMB-320/321-E) S-052	64,915
1	Regulatory	US	6/23/2004	Book 47	FDA Submission - IND	L. Weissberger- Protocol Amendment- New Investigators – A. Waxman, P. Corris, A. Peacock, J. Pepke-Zaba, J. Gossage, J. Klinger, K. Mubarak, S. Murali (AMB-320, AMB-321, AMB-320/321-E) S-051	64,915
1	Regulatory	US	5/27/2004	Book 47	FDA Correspondence - Letter	FDA Contact Report -AMB Orphan Drug Application - Amendment - Reference Number: 04-1836	64,915
1	Regulatory	US	5/7/2004	Book 47	FDA Submission - IND	L. Weissberger- Protocol Amendment: New Investigators R. Allen, S. Murali, R. Oudiz, J. Wirth, J. Behr, J. Albert Barbera, C. Black, R. Channick, M. McGoan, F. Torres (AMB-320, AMB-321, AMB-320/321-E) S-050	64,915
1	Regulatory	US	5/6/2004	Book 46	FDA Submission - IND	L. Weissberger- Protocol Amendment: Change in Protocols: 320, 321, 320/321-E. S-049	64,915

1	Regulatory	US	5/3/2004	Book 46	FDA Correspondence - Phone call	FDA Contact Report - Call to Melissa Robb. Subject: To discuss darusentan submission & PK program for ambrisentan.	2004-05- BERGER_MROBB.pdf	64,915
1	Regulatory	US	4/28/2004	Book 46	FDA Correspondence - Phone call	FDA Contact Report - Call to Brad Glasscock, Tan Nguyen. Subject: To clarify request for information from Brad Glasscock.	2004-04- BERGER_GLASSCOCK.pdf	64,915
1	Regulatory	US	4/22/2004	Book 46	FDA Correspondence - Email	FDA Contact Report - Email. L. Weissberger/P. Marroun. Email with attached word document - Feedback on Proposed Changes to AMB-320/321-E.	2004-04- 22_64915_CORR_EMAIL_LWEISSBERGER_PMARROUM.pdf	64,915
1	Regulatory	US	4/21/2004	Book 46	FDA Correspondence - Phone call	FDA Contact Report - Dr. Glasscock called to inquire as to the status of the requested amendment.	2004-04- 21_64915_CORR_PHONE_BGLASC_OCK_LWEISSBERGER.pdf	64,915
1	Regulatory	US	4/12/2004	Book 46	FDA Submission - IND	Protocol Amendment - L. Weissberger- New Investigators J. Edelman, J. Mandel, M. Park, R. Schilz, H. Olschewski (AMB-320, AMB-321, AMB-320/321-E) S-048	S-048	64,915
1	Regulatory	US	4/8/2004	Book 46	FDA Correspondence - Phone call	FDA Contact Report- Call to Jeffrey Fritsch to inquire the status of application - J. Fritsch was out of office and Mary Grice answered questions.	2004-04- 08_64915_CORR_PHONE_LWEISSBERGER_BGLASSCOCK.pdf	64,915
1	Regulatory	US	4/7/2004	Book 46	FDA Correspondence - Phone call	FDA Contact Report- Comments on proposed changes to extension protocol - pop. K and PK sub study.	2004-04- 07_64915_CORR_PHONE_LWEISSBERGER_MROBB.pdf	64,915
1	Regulatory	US	3/26/2004	Book 45	FDA Submission - IND	Protocol Amendment - L. Weissberger- New Investigators- N. Hill, C. Jennings, M. McGoan, D. Zwicke, S. Maruti Bhorade (AMB-320, AMB-321, AMB-320/321-E) S-047	S-047	64,915
1	Regulatory	US	3/25/2004	Book 45	FDA Submission - IND	L. Weissberger-Type C Meeting Request. S-046	S-046	64,915
1	Regulatory	US	3/17/2004	Book 45	FDA Submission - IND	L. Weissberger- Pharmacology/Toxicology 2-Year Rat and Mouse Final Protocols. S-045	S-045	64,915

1	Regulatory	US	3/5/2004	Book 45	FDA Submission - IND	Protocol Amendment - L. Weissberger- New Investigators- D. Badesch, R. Foley, E. Lawrence, I. Robbins, S. Shapiro (AMB-320) S- 044	S-044	64,915
1	Regulatory	US	2/27/2004	Book 44	FDA Submission - IND	Protocol Amendment - L. Weissberger- New Investigators- R. Channick, K. Mubarak, F. Torres, R. Naeija, N. Galie, A. Keogh (AMB- 320, AMB-321, AMB-320/321-E) S- 043	S-043	64,915
1	Regulatory	US	2/24/2004	Book 44	FDA Correspondence - Fax	Response to Carcinogenicity Protocol Assessment Request - Final CAC Report.	2004-02- 24_64915_CORR_FAX_SEIFRIED_- WALDO.pdf	64,915
1	Regulatory	US	2/24/2004	Book 44	FDA Correspondence - Letter	J. Fritsch- Acknowledge receipt of application for orphan designation submitted.	2004-02- 24_ODA_US_CORR LETTER_ASSI- GN_ODA_NUMBER.pdf	64,915
1	Regulatory	UK	2/20/2004	Book 44	Foreign Correspondence - MHRA	Clinical Trial Application UK - MHRA-Exemption from licenses.	2004-02- 20_64915_MHRA_CORR LETTER. pdf	64,915
1	Regulatory	US	2/16/2004	Book 44	FDA Submission - IND	Protocol Amendment - L. Weissberger- New Investigators- J. Gossage, M. Delcroix, G. Simonneau, F. Xaver Kleber, J. Ben- Dov, and P. Engel (AMB-320, AMB- 321, AMB-320/321-E) S-042	S-042	64,915
1	Regulatory	US	2/13/2004	Book 44	FDA Submission - IND	L. Weissberger-Information Amendment- Updated IB.	S-041	64,915
1	Regulatory	US	1/30/2004	Book 44	FDA Submission - IND	L. Weissberger-Change in US Agent from Quintiles, Inc. to Myogen, Inc.	S-040	64,915
1	Regulatory	US	1/28/2004	Book 44	FDA Correspondence - Fax	Fax - Response to Carcinogenicity Protocol Assessment Request - Final CAC Report.	2004-01- 28_64915_CORR_FAX_FDA.pdf	64,915
1	Regulatory	US	1/16/2004	Book 44	FDA Correspondence - Fax	Z. McDonald- Receipt of request - Serial No. 036 for a special carcinogenicity protocol assessment.	2004-01- 16_64915_CORR_FAX_FDA.pdf	64,915

1	Regulatory	US	1/15/2004	Book 44	FDA Submission - IND	Protocol Amendment - New Investigators-R. Fairman, M. Robbins, H. Garcia (AMB-320, AMB-320/321-E) S-039	S-039	64,915
1	Regulatory	US	1/14/2004	Book 44	FDA Correspondence - Email	Email Communication regarding special assessment for 2-year mouse carcinogenicity protocol.	2004-01-14_64915_CORR_EMAIL_CWALDO_MROBB.pdf	64,915
1	Regulatory	US	1/12/2004	Book 44	FDA Submission - IND	Courtesy copy of Orphan Drug Application (Cover Letter) S-038	S-038	64,915
1	Regulatory	US	1/6/2004	Book 44	FDA Submission - IND	Protocol Amendment - New Investigators- Keogh, Baratz, Engel, Garcia, Klinger (AMB-320-E) S-037	S-037	64,915
1	Regulatory	US			FDA Correspondence - Letter	Letter from - M. Gerber to Dr. Haffner about transfer of responsibility as US Agent and Authorized Representative effective Dec. 12, 2003, quintiles, Inc. assumes the responsibility from Myogen, Inc. as the US Agent to interact with the office of Orphan Products Development	2004-01-05_64915_CORR LETTER_HAFNE_R_WALDO.pdf	64,915
1	Regulatory	US	1/5/2004	Book 44	FDA Correspondence - Letter	Letter from- C. Wirth to Dr. Haffner regarding registration for 2003-01-01, FDA WIR, WAF, FDC, pdf	2004-01-05_64915_CORR LETTER_HAFNE_R_WALDO.pdf	64,915
1	Regulatory	US	12/18/2003	Book 43	FDA Submission - IND	Request for Special Protocol Assessment 2-Year Mouse Carcinogenicity Protocol. S-036	S-036	64,915
1	Regulatory	US	12/2/2003	Book 43	FDA Submission - IND	Change in Protocol: 220-E. S-035	S-035	64,915
1	Regulatory	US	11/24/2003	Book 43	FDA Correspondence - Fax	FDA Contact Report. Fax. Subject: Response to Carcinogenicity Protocol Assessment Request - Final CAC Report - IND 64,915	2003-11-24_64915_CORR_FAX_SEIIRIED_WALDO.pdf	64,915
1	Regulatory	US	10/20/2003	Book 43	FDA Correspondence - Letter	FDA Contact Report-Z. McDonald-Acknowledgement of receipt from Oct. 13, 2003, request for a special carcinogenicity protocol assessment.	2003-10-20_64915_CORR LETTER_ZMCDO_NALD_MGERBER.pdf	64,915
1	Regulatory	US	10/13/2003	Book 43	FDA Submission - IND	Request for special protocol assessment 2-Year Rat Carcinogenicity Protocol. S-034	S-034	64,915

1	Regulatory	US	10/9/2003	Book 42	FDA Correspondence - Phone call	FDA Contact Report- Response to questions.	2003-10-	09_64915_CORR_PHONE_CWALD_O_MROBB.pdf	64,915
1	Regulatory	US	10/8/2003	Book 42	FDA Correspondence - Email	C. Waldo-Response to Carcinogenicity Protocol Assessment Request.	2003-10-	08_64915_CORR_EMAIL_CWALD_O_MROBB.pdf	64,915
1	Regulatory	US	10/8/2003	Book 42	FDA Submission - IND	New Phase III Protocols: 320, 321, 320/321-E Response Requested. S-033		S-033	64,915
1	Regulatory	US	10/7/2003	Book 42	FDA Correspondence - Email	FDA Contact Report- Email - Phase III- Protocols. C. Waldo.	2003-10-	07_64915_CORR_EMAIL_CWALD_O_MROBB.pdf	64,915
1	Regulatory	US	10/7/2003	Book 42	FDA Correspondence - Phone call	FDA Contact Report- Regarding request for feedback.	2003-10-	07_64915_CORR_PHONE_CWALD_O_ROBB.pdf	64,915
1	Regulatory	US	10/7/2003	Book 42	FDA Correspondence - Phone call	FDA Contact Report- Phone call - Left v-mail regarding request for feedback.	2003-10-	07A_64915_CORR_PHONE_ROBB_WALDO.pdf	64,915
1	Regulatory	US	9/9/2003	Book 42	FDA Correspondence - Fax	FDA Correspondence - Fax - 8/27/03 Meeting Minutes.	2003-09-	09_64915_CORR_FAX_ROBB_WALDO.pdf	64,915
1	Regulatory	US	9/9/2003	Book 42	FDA Correspondence - Phone call	FDA Contact Report- Confirm receipt of fax containing the meeting minutes from the 8/27/2003 meeting with the division.	2003-09-	09_64915_CORR_PHONE_ROBB_WALDO.pdf	64,915
1	Regulatory	US	9/9/2003	Book 42	FDA Submission - IND	Protocol Amendment: New investigators: D. Badesch, M. McGroon, S. Rich, M. Landzberg, R. Barst (AMB-220-E) S-032		S-032	64,915
1	Regulatory	US	9/4/2003	Book 42	FDA Correspondence - Phone call	FDA Contact Report-Special Protocol Assessment.	2003-09-	04_64915_CORR_PHONE_CWALD_O_MROBB.pdf	64,915
1	Regulatory	US	9/3/2003	Book 42	FDA Submission - IND	IND Annual Report. S-031		S-031	64,915
1	Regulatory	US	8/27/2003	Book 41	FDA Correspondence - Phone call	FDA Contact Report- Verify FDA meeting attendees.	2003-08-	27_64915_CORR_PHONE_CWALD_O_MROBB.pdf	64,915
1	Regulatory	US	8/27/2003	Book 41	FDA Correspondence - Meeting	Meeting Minutes from - August 27, 2003 meeting with FDA.	2003-08-	27_64915_CORR_MEETING_CWALD_O_MROBB.pdf	64,915

1	Regulatory	US	8/22/2003	Book 41	FDA Correspondence - Phone call	FDA Contact Report- End of Phase II Meeting.	2003-08-	22_64915_CORR_PHONE_CWALD_O_MROBB.pdf	64,915
1	Regulatory	US	8/8/2003	Book 41	FDA Correspondence - Phone call	FDA Contact Report- Copies for August 27 Meeting.	2003-08-	08_64915_CORR_PHONE_CWALD_O_MROBB.pdf	64,915
1	Regulatory	US	8/8/2003	Book 41	FDA Correspondence - Letter	FDA Correspondence - Letter - 4 Additional copies of the info. Package for 8/27/03 meeting.	2003-08-	08_64915_CORR LETTER_INFO_PKG_COPIES.pdf	64,915
1	Regulatory	US	8/7/2003	Book 41	FDA Correspondence - Phone call	FDA Contact Report- Confirm FDA receipt of Briefing Document for August 27 Meeting.	2003-08-	07_64915_CORR_PHONE_CWALD_O_MROBB.pdf	64,915
1	Regulatory	US	8/5/2003	Book 41	FDA Correspondence - Phone call	FDA Contact Report-End of Phase II briefing package.	2003-08-	05_64915_CORR_PHONE_MROBB_CWALDO.pdf	64,915
1	Regulatory	US	8/5/2003	Book 41	FDA Submission - IND	Information Package for August 27, 2003 Meeting.	S-030		64,915
1	Regulatory	US	7/25/2003	Book 41	FDA Submission - IND	Protocol Amendment: New Investigators: Teresa De Marco (AMB-220-E) S-029	S-029		64,915
1	Regulatory	US	7/10/2003	Book 41	FDA Submission - IND	FDA - General Correspondence - Contact Information. S-028	S-028		64,915
1	Regulatory	US	7/8/2003	Book 41	FDA Correspondence - Fax	FDA Contact Report -Confirmation of Meeting g. August 27, 2003	2003-07-	08_64915_CORR_FAX_MROBB_ME_NLOW.pdf	64,915
1	Regulatory	US	7/7/2003	Book 41	FDA Submission - IND	Protocol Amendment: New Investigators-I. Robbins, S. Shapiro, AMB-220-E. S-027	S-027		64,915
1	Regulatory	US	7/2/2003	Book 41	FDA Submission - IND	Meeting Request: Type B. Request for Re-Scheduling. S-026	S-026		64,915
1	Regulatory	US	7/2/2003	Book 41	FDA Correspondence - Phone call	FDA Contact Report- M. Robb requested that we resubmit the request to reschedule the end of phase II meeting for IND 64,915	2003-07-	02_64915_CORR_PHONE_MENLOW.pdf	64,915
1	Regulatory	US	6/26/2003	Book 41	FDA Correspondence - Phone call	FDA Contact Report-R. Fortney checked on request to re-schedule the end-of Phase II meeting with Melissa Robb.	2003-06-	26_64915_CORR_PHONE_RFORTN_EY_MENLOW.pdf	64,915

		US	6/24/2003	Book 41	FDA Submission - IND	IND - Meeting Request - Type B Request for Re-Scheduling S-025	S-025	64,915
1	Regulatory	US	6/23/2003	Book 41	FDA Correspondence - Phone call	FDA Contact Report- M.Robb requested that the end of Phase II meeting originally scheduled for July 11, 2003 be re-scheduled.	2003-06- 23_64915_CORR_PHONE_MENLO W_MROBB.pdf	64,915
1	Regulatory	US	6/13/2003	Book 41	FDA Submission - IND	Protocol Amendment: New Investigators and Revision to FDA form 1572 (AMB-220-E) S-024	S-024	64,915
1	Regulatory	US	5/23/2003	Book 40	FDA Correspondence - Fax	FDA Contact Report-Fax - Confirmation of 7/11/03.	2003-05- 23_64915_CORR_FAX_MROBB_ME NLLOW.pdf	64,915
1	Regulatory	US	5/15/2003	Book 40	FDA Correspondence - Phone call	FDA Contact Report- M. Robb called Project Manager to confirm receipt of fax	2003-05- 23_64915_CORR_PHONE_ATANNE R_MROBB.pdf	64,915
1	Regulatory	US	5/15/2003	Book 40	FDA Correspondence - Fax	FDA Correspondence - Fax - Formal meeting request for an End of Phase II meeting.	2003-05- 15_64915_CORR_FAX_MENLOW_- MROBB.pdf	64,915
1	Regulatory	US	5/15/2003	Book 40	FDA Submission - IND	Meeting Request : Type B. S-023	S-023	64,915
1	Regulatory	US	5/6/2003	Book 40	FDA Submission - IND	Protocol Amendment- New Investigators. S-022	S-022	64,915
1	Regulatory	US	5/2/2003	Book 40	FDA Submission - IND	IND Safety Report - Follow-up IND Safety Report Mfg. Rpt. No. 29404 (Follow-up 1) S-021	S-021	64,915
1	Regulatory	US	4/22/2003	Book 40	FDA Submission - IND	General Correspondence - Transfer of Regulatory Obligations. S-020	S-020	64,915
1	Regulatory	US	4/1/2003	Book 40	FDA Submission - IND	General Correspondence - Duration of Chronic Toxicity Study. M. Enlow/D. Throckmorton. S-019	S-019	64,915
1	Regulatory	US	3/20/2003	Book 40	FDA Correspondence - Phone call	FDA Contact Report: Inquire about letter of intent for submission of Special Carcinogenicity Protocol submission.	2003-03- 20_64915_CORR_PHONE_MENLO W_MROBB.pdf	64,915

1	Regulatory	US	3/19/2003	Book 40	FDA Submission - IND	General Correspondence - Copy of letter to investigators regarding two deaths (unrelated) and consent form changes. M.Enlow/D.Throckmorton. S-018	64,915
1	Regulatory	US	3/11/2003	Book 40	FDA Submission - IND	General Correspondence - Copy of Investigator Notification of IND Safety Report for elevated Liver Function Tests. M.Enlow/D.Throckmorton. S-017	64,915
1	Regulatory	US	3/10/2003	Book 40	FDA Correspondence - Phone call	FDA Contact Report: Express concern that report of elevated LFTs to greater than 8 times upper limit of normal was not initially considered a SAE and suggest the sponsors remind investigators of potential for hepatotoxicity and need for SAE reporting of such event. JPelayo, MD/M.Enlow.	64,915
1	Regulatory	US	3/7/2003	Book 40	FDA Correspondence - Phone call	FDA Contact Report: Project Manager communicates FDA decision on extension protocol AMB-220-E. L.Tanner/M.Robb.	2003-03-10_64915_CORR_PHONE_JPELAYO_MENLOW.pdf
1	Regulatory	US	3/5/2003	Book 40	FDA Submission - IND	IND 15-Day ADR Report. M. Enlow/FDA. S-016	2003-03-07_64915_CORR_PHONE_MROBB_ATANNER.pdf
1	Regulatory	US	3/5/2003	Book 40	FDA Correspondence - Fax	FDA Correspondence - Fax of submission dated 3/5/03 S-016.	2003-03-05_64915_CORR_FAX_MENLOW_MROBB.pdf
1	Regulatory	US	2/28/2003	Book 40	FDA Correspondence - Phone call	FDA Contact Report: Discuss case of increased liver function tests reported in study AMB-220.	2003-02-28_64915_CORR_PHONE_MENLOW_MROBB.pdf
1	Regulatory	US	2/27/2003	Book 40	FDA Correspondence - Phone call	FDA Contact Report: Check status of Division's review of extension Protocol, AMB-220-E. M. Enlow/M. Robb	2003-02-27_64915_CORR_PHONE_MENLOW_MROBB.pdf
1	Regulatory	US	2/11/2003	Book 40	FDA Correspondence - Phone call	FDA Contact Report: Discuss Typo's of year submitted on Protocol AMB220-E.	2003-02-11_64915_CORR_PHONE_MENLOW_MROBB.pdf
1	Regulatory	US	2/7/2003	Book 40	FDA Submission - IND	Protocol Amendment: New Protocol AMB 220-E. S-015	64,915

1	Regulatory	US	2/5/2003	Book 40	FDA Submission - IND	Protocol Amendment: New Investigators -McGoon, Landzberg, Marco. S-014	S-014	64,915
1	Regulatory	US	1/27/2003	Book 40	FDA Correspondence - Phone call	FDA Contact Report: Inform sponsors the Division is still discussing internally the open-label extension study, protocol AMB-222, and timing relative to the non-rodent chronic toxicity study.	27 _64915_CORR_PHONE_MROBB_MENLOW.pdf	64,915
1	Regulatory	US	1/24/2003	Book 40	FDA Correspondence - Phone call	FDA Contact Report: Discuss open-label extension study, protocol AMB-222, and timing relative to non-rodent chronic toxicity study. M. Robb & M. Enlow	20 _64915_CORR_PHONE_MROBB_MENLOW.pdf	64,915
1	Regulatory	US	1/20/2003	Book 40	FDA Correspondence - Phone call	FDA Contact Report: Message left-update on feedback request for proposal to provide open-label treatment beyond 24 wks.	20 _64915_CORR_PHONE_MENLO_W_MROBB.pdf	64,915
1	Regulatory	US	1/14/2003	Book 40	FDA Submission - IND	Response to FDA Request - submitting safety monitoring plans for 12-wk Open-label Extension Period for AMB 220 and draft safety monitoring plans for AMB 222. S-013	S-013	64,915
1	Regulatory	US	1/14/2003	Book 40	FDA Correspondence - Phone call	FDA Contact Report - Confirm 12-wk extension period in Protocol AMB-220 could proceed.	14 _64915_CORR_PHONE_MROBB_MENLOW.pdf	64,915
1	Regulatory	US	1/13/2003	Book 40	FDA Correspondence - Phone call	FDA Contact Report - FDA Project Manager called to request additional IND 64,915 information. M. Robb and A. Tanner	13 _64915_CORR_PHONE_MROBB_ATANNER.pdf	64,915
1	Regulatory	US	1/13/2003	Book 40	FDA Correspondence - Fax	FDA Contact Report - Fax - Response to FDA Request for additional information regarding IND 64,915.	13 _64915_CORR_FAX_TANNER_MROBB.pdf	64,915
1	Regulatory	US	1/10/2003	Book 40	FDA Correspondence - Phone call	FDA Contact Report - Discuss causes of death in some animals in 26-wk rat toxicity study. M. Enlow & W. Link.	64915_CORR_PHONE_MENLOW_M	64,915
1	Regulatory	US	1/10/2003	Book 40	FDA Correspondence - Phone call	FDA Contact Report - Inquire whether Melissa could provide update on Division's position on the explanation given for mortality in 26 wk rat toxicity study and moving into the extension phase of the clinical study.	10A _64915_CORR_PHONE_MENLOW_MROBB.pdf	64,915

1	Regulatory	US	1/9/2003	Book 40	FDA Correspondence - Phone call	FDA Contact Report - Clarify their internal mtg. to discuss 26-wk toxicity studies & open-label extensions to the clinical study.	09_64915_CORR_PHONE_MROBB_MENLOW.pdf	64,915
1	Regulatory	US	1/9/2003	Book 40	FDA Submission - IND	Protocol Amendment - New Investigators: AMB-220 Simonneau, France; McLaughlin, Robbins, & Shapiro, United States. S-012		64,915
1	Regulatory	US	1/9/2003	Book 40	FDA Correspondence - Phone call	FDA Contact Report - Arrange time for phone conference to discuss questions about he 26-wk toxicity study. W. Link, M. Enlow	09_64915_CORR_PHONE_MENLO_W_WLINK.pdf	64,915
1	Regulatory	US	1/8/2003	Book 40	FDA Correspondence - Phone call	FDA Contact Report - To clarify the date of their internal meeting to discuss the 26-week toxicity studies and the open-label extensions to the clinical study.	08_64915_CORR_PHONE_MENLO_W_MROBB.pdf	64,915
1	Regulatory	US	1/2/2003	Book 40	FDA Submission - IND	General Correspondence - Rationale & Study Summary for additional long-term protocol. From Quintiles to Dr. Throckmorton. S-011		64,915
1	Regulatory	US	1/2/2003	Book 40	FDA Correspondence - Phone call	FDA Contact Report - Informed Melissa Robb that faxed copy of submission w- Rationale & Study Summary for Protocol AMB-222 sent.	02_64915_CORR_PHONE_MENLO_W_MROBB.pdf	64,915
1	Regulatory	US	12/23/2002	Book 40	FDA Correspondence - Fax	FDA Contact Report - Fax - Copy of authorization with information and study summary (S-011)	02_64915_CORR_PHONE_MENLO_W_MROBB.pdf	64,915
1	Regulatory	US	12/30/2002	Book 2	FDA Correspondence - Phone call	FDA Contact Report - Follow-up regarding extension of treatment beyond 6 months.	30_64915_CORR_PHONE_ENLOW_ROBB.pdf	64,915
1	Regulatory	US	12/24/2002	Book 2	FDA Correspondence - Phone call	FDA Contact Report - Follow-up regarding extension of treatment beyond 6 months.	24_64915_CORR_PHONE_MROBB_MENLOW.pdf	64,915
1	Regulatory	US	12/23/2002	Book 2	FDA Correspondence - Phone call	FDA Contact Report - Inquire about date of Division's Internal mtg. To discuss 26 wk toxicity studies and whether Division would consider clinical extension protocol for treatment beyond 6 months.	23_64915_CORR_PHONE_MENLO_W_MROBB.pdf	64,915

1	Regulatory	US	12/12/2002	Book 2	FDA Correspondence - Phone call	FDA Contact Report – Informed Quintiles that the Division scheduled an internal mtg. In January 2003 to discuss 26 wk toxicology studies.	2002-12- 12_64915_CORR_PHONE_MROBB_- MENLOW.pdf	64,915
1	Regulatory	US	12/11/2002	Book 2	FDA Correspondence - Phone call	FDA Contact Report – Informed Melissa Robb, new FDA project mgr. That the 26 wk toxicity study submitted and receipt confirmed.	2002-12- 11_64915_CORR_PHONE_MENLO_W_MROBB.pdf	64,915
1	Regulatory	US	12/10/2002	Book 2	FDA Correspondence - Phone call	FDA Contact Report – Informed Zelda that 26 wk toxicology draft study report submitted. Zelda to provide name & phone # of new FDA project mgr for IND.	2002-12- 10_64915_CORR_PHONE_MENLO_W_ZMCDONALD.pdf	64,915
1	Regulatory	US	12/9/2002	Book 34-39	FDA Submission - IND	Vol. 1 - 6 - Response to FDA Request for Information - 26 wk. Toxicity Studies (Draft Reports: Dog and Rat) S-010	S-010	64,915
1	Regulatory	US	11/8/2002	Book 2	FDA Submission - IND	Protocol Amendment - New Investigators – Olschewski, Schiltz, Germany and United States (AMB-220) S-009	S-009	64,915
1	Regulatory	US	11/6/2002	Book 2	FDA Submission - IND	Information Amendment: Clinical. S-008	S-008	64,915
1	Regulatory	US	10/29/2002	Book 1	FDA Submission - IND	Response to FDA Request for Information – Chemistry, Manufacturing & Controls. S-007	S-007	64,915
1	Regulatory	US	10/18/2002	Book 1	FDA Submission - IND	New Investigators – Keogh, Naeije, Hooper, Galie, Rubin, Frost, Zwicke, Australia, Belgium, Germany, Italy and United States (AMB-220) S-006	S-006	64,915
1	Regulatory	US	9/25/2002	Book 1	FDA Submission - IND	Protocol Amendment – New Investigators – DBadesch and Rdoyle (AMB-220) S-005	S-005	64,915
1	Regulatory	US	9/20/2002	Book 1	FDA Correspondence - Letter	FDA Contact Report – FDA completed chemistry review of 7-17-2002 (S-002) submission & provided comments-requests. Dthrockmorton-JMFreytag-Myogen Menlow.	2002-09- 20_64915_CORR LETTER_DTHRO_CKMORTON_WFREYTAG.pdf	64,915
1	Regulatory	US	9/10/2002	Book 1	FDA Submission - IND	Protocol Amendment – New Investigators US: ROudiz 004 (AMB-220) - S-004	S-004	64,915

1	Regulatory	US	8/30/2002	Book 1	FDA Submission - IND	Protocol Amendment - Submitted Amendment 1, dated 7-26-2002 for Protocol No. AMB-220 (No Suggestions) - S-003	S-003	64,915
1	Regulatory	US	7/31/2002	Book 1	FDA Correspondence - Letter	FDA Contact Report - Letter from FDA with regard to Clinical Trials Data Bank, asking for review of protocol submitted with S-000 to determine if it is a trial for a serious disease or condition and if it is a trial to test effectiveness	2002-07- 31_64915_CORR LETTER_JWOOD COCK_CKIRK.pdf	64,915
1	Regulatory	US	7/17/2002	Book 33	FDA Submission - IND	Information Amendment: Amendment to provide updated info for drug substance and drug product. (CHEMISTRY) - S-002	S-002	64,915
1	Regulatory	US	6/28/2002	Book 1	FDA Submission - IND	Information Amendment: Clinical Revised Informed Consent Form - S- 001	S-001	64,915
1	Regulatory	US	6/28/2002	Book 1	FDA Correspondence - Fax	FDA Contact Report - Inform Zelda a revised Informed Consent form for Protocol AMB-220 was being sent to her as requested by Dr. Stockbridge.	2002-06- 28_64915_CORR_FAX_MENLOW_Z MCDONALD.pdf	64,915
1	Regulatory	US	6/28/2002	Book 1	FDA Correspondence - Phone call	FDA Contact Report - Inform Zelda a revised Informed Consent form for Protocol AMB-220 was being sent to her as requested by Dr. Stockbridge.	2002-06- 28_64915_CORR_PHONE_MENLO W_ZMCDONALD.pdf	64,915
1	Regulatory	US	6/25/2002	Book 1	FDA Correspondence - Phone call	FDA Contact Report - Request Chg to Informed Consent document & discuss Pharm-Tox required for supporting open-label extension study.	2002-06- 25_64915_CORR_PHONE_NSTOCK BRIDGE_MENLOW.pdf	64,915
1	Regulatory	US	6/25/2002	Book 1	FDA Correspondence - Phone call	FDA Contact Report - Called Monica Cooper to discuss questions about stability data for the drug product.	2002-06- 25_64915_CORR_PHONE_MENLO W_MCOOPER.pdf	64,915
1	Regulatory	US	6/24/2002	Book 1	FDA Correspondence - Phone call	FDA Contact Report - Monica Cooper call Marguerite -asked a few questions about the stability data for the drug product.	2002-06- 24_64915_CORR_PHONE_MCOOP ER_MENLOW.pdf	64,915
1	Regulatory	US	6/10/2002	Book 1	FDA Correspondence - Letter	FDA Correspondence - Letter - Acknowledgement of receipt of IND Application submitted.	2002-06- 10_64915_CORR LETTER_ZMCDO NALD_WFREYTAG.pdf	

1	Regulatory	US	6/6/2002	Book 1	FDA Correspondence - Phone call	FDA Contact Report - To check- confirm receipt by Zelda of IND Submission.	2002-06- 06_64915_CORR_PHONE_ZMCDO NALD_MENLOW.pdf	64,915
1	Regulatory	US	6/3/2002	Book 1	FDA Correspondence - Phone call	FDA Contact Report - Inform Zelda BSF 208075 IND for PAH was shipped to FDA on June 3, 2002.	2002-06- 03_64915_CORR_PHONE_MENLO W_ZMCDONALD.pdf	64,915
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Ambrisentan: Pulmonary Arterial Hypertension - NDA 22-081 - CORRESPONDENCE									
LINK TO NDA AMENDMENTS									
LINK TO NDA AMENDMENTS									
1	Regulatory	US	7/20/2007	Temp 6	FDA Correspondence - Phone	H.Isokoski/D.Brum - phone call. Subject: Spanish translations of the RiskMAP tools. New reminder tools for LEAP. Correct address for waiver request for MedWatch forms for non-serious and labeled adverse events (Aes)	2007-07-20_22081_CORR_PHONE_HISOKOSKI_DB_BRUM.pdf	22-081	
1	Regulatory	US	7/20/2007	Temp 6	FDA Correspondence - Email	D.Brum - 7/20/2007 on foreign language translation.	20_22081_CORR_EMAIL_HISOKOSKI_DB_RUM.pdf	22-081	
1	Regulatory	US	7/16/2007	Temp 6	FDA Correspondence - Email	D.Brum/H.Isokoski - Postmarketing Study Commitment Correspondence and Patent Information. NDA 22-081	16_22081_CORR_EMAIL_HISOKOSKI_DB_RUM.pdf	22-081	
1	Regulatory	US	7/13/2007	Temp 6	FDA Correspondence - Email	D.Brum/H.Isokoski - Postmarketing Study Commitment Correspondence and Patent Information. NDA 22-081	13_22081_CORR_EMAIL_HISOKOSKI_DB_RUM.pdf	22-081	
1	Regulatory	US	7/11/2007	Temp 6	FDA Correspondence - Phone	D.Brum/H.Isokoski - Letairis RiskMAP. To update the Division on the status of the submission and seek their advice on correct process.	11_22081_CORR_PHONE_HISOKOSKI_DB_BRUM.pdf	22-081	
1	Regulatory	US	7/11/2007	Temp 6	FDA Correspondence - Email	D.Brum/H.Isokoski - Letairis RiskMAP.	11_22081_CORR_EMAIL_HISOKOSKI_DB_RUM.pdf	22-081	
1	Regulatory	US	7/9/2007	Temp 6	FDA Correspondence - Phone	T.Marshall/T.Bouie - Phone calls on June 21, June 29 and July 9, 2007. Subject: Post-Approval Supplement for Change to RPM in Dissolution Method. NDA 22-081	2007-07-09_22081_CORR_PHONE_TBOUIE_TMAR SHALL.pdf	22-081	

1	Regulatory	US	7/9/2007	Temp 6	FDA Correspondence - Email T.Marshall/T.Bouie - Teleconference (July 10) information with the list of attendees from Gilead and FDA attendees. NDA 22-081 for Letairis Tablets-Proposal for CBE-30 Post Approval Supplement-Increase in Dissolution Method Paddle Speed.	22-081	2007-07-	09_22081_CORR_EMAIL_TMARSHALL_T_BOUIE.pdf
1	Regulatory	US	7/6/2007	Temp 6	FDA Correspondence - Email L.Tanner/D.Brum - Notification of Last Day at Gilead.	22-081	2007-07-	06_22081_CORR_EMAIL_LTANNER_DBR_UM.pdf
1	Regulatory	US	7/3/2007	Temp 6	FDA Correspondence - Email L.Tanner/D.Brum - Respond from D.Brum to the questions regarding the Revising RiskMAP and Materials to Reflect "Prescriber"	22-081	2007-07-	03_22081_CORR_EMAIL_LTANNER_DBR_UM.pdf
1	Regulatory	US	7/2/2007	Temp 6	FDA Correspondence - Email L.Tanner/D.Brum - Subject: Pediatric Plan. Revisions to RiskMAP and educational materials.	22-081	2007-07-	02_22081_CORR_PHONE_LTANNER_DBR_UM.pdf
1	Regulatory	US	7/2/2007	Temp 6	FDA Correspondence - Email L.Tanner/D.Brum - Proposed Plan for Revising RiskMAP and Materials to Reflect "Prescriber"	22-081	2007-07-	02_22081_CORR_EMAIL_LTANNER_DBR_UM.pdf
1	Regulatory	US	6/22/2007	Temp 6	FDA Correspondence - Email T.Marshall/T.Bouie - Proposal for CBE-30 Post Approval Supplement_Increase in Dissolution Method Paddle Speed. NDA 22-081	22-081	2007-06-	22_22081_CORR_EMAIL_TBOUIE_TMAR SHALL.pdf
1	Regulatory	US	6/21/2007	Temp 6	FDA Correspondence - Email T.Marshall/S.Goldie - Post-Approval Supplement for Change to RPM in Dissolution Method. NDA 22-081	22-081	2007-06-	21_22081_CORR_PHONE_TMARSHALL_S_GOLDIE.pdf
1	Regulatory	US	6/19/2007	Temp 6	FDA Correspondence - L.Tanner/D.Brum - Subject: Administrative process for post-approval submissions of PI to the NDA	22-081	2007-06-	19_22081_CORR_PHONE_LTANNER_DBR_UM.pdf
1	Regulatory	US	6/15/2007	Temp 6	FDA Correspondence - L.Tanner/D.Brum - Subject: Final processes for approval. NDA 22-081	22-081	2007-06-	15_22081_CORR_PHONE_LTANNER_DBR_UM.pdf
1	Regulatory	US	6/15/2007	Temp 6	FDA Correspondence - Letter R.Temple/L.Tanner - The NDA 22-081 - Letairis, Approval Letter from FDA. PI attached.	22-081	2007-06-	15_22081_CORR LETTER_RTEMPLE_LTANNER.pdf
1	Regulatory	US	6/15/2007	Temp 6	Internal Correspondence - Labeling Approval - RAAN CMC - Approved in the US on June 15, 2007	22-081	2007-06-	15_22081_CORR_RAAN_NOTIFICATION.pdf

1	Regulatory	US	6/14/2007	Temp 6	FDA Correspondence - Phone	L.Tanner/D.Brum, T.Marciniak, J.Hung - Resolve remaining issues with PI.	2007-06-14_22081_CORR_PHONE_LTANNER_DBR_UM.pdf	22-081
1	Regulatory	US	6/13/2007	Temp 6	FDA Correspondence - Phone	L.Tanner/D.Brum - Issues with opening files during Label Negotiation. Cancellation of teleconference between Gilead and FDA.	2007-06-13_22081_CORR_PHONE_LTANNER_DBR_UM.pdf	22-081
1	Regulatory	US	6/12/2007	Temp 6	FDA Correspondence - Phone	L.Tanner/D.Brum, J.Weaver, S.Berkman - Remaining issues with the RiskMAP	2007-06-12_22081_CORR_PHONE_LTANNER_DBR_UM_2.pdf	22-081
1	Regulatory	US	6/12/2007	Temp 6	FDA Correspondence - Phone	L.Tanner/D.Brum - Final inspection report for Site #207 (Nazzareno Galie) Italy. Next steps for submitting Gilead comments for PI. Teleconference with FDA on Wednesday, 13 June 2007. Teleconference to discuss cyclosporine contraindication.	2007-06-12_22081_CORR_PHONE_LTANNER_DBR_UM.pdf	22-081
1	Regulatory	US	6/11/2007	Temp 6	FDA Correspondence - Phone	L.Tanner/T.Marciniak - Feedback regarding FDA comments to PI.	2007-06-11_22081_CORR_PHONE_LTANNER_TM_ARCINIAK.pdf	22-081
1	Regulatory	US	6/11/2007	Temp 6	FDA Correspondence - Phone	L.Tanner/R.Fortney - The phone calls (6/8/2007 & 6-11-2007) to proactively schedule teleconference to resolve any remaining NDA issues, particularly with the PI.	2007-06-11_22081_CORR_PHONE_LTANNER_RFO_RTNEY.pdf	22-081
1	Regulatory	US	6/11/2007	Temp 6	FDA Correspondence - Email T.Marshall/G.Scott - Attachment NDA 22-081 Amend 019. Summary of CMC Agreements Reached During June 8, 2007 CMC Teleconference	2007-06-11_22081_CORR_EMAIL_SGOLDIE_TMA_RSHALL.pdf	22-081	
1	Regulatory	US	6/11/2007	Temp 6	FDA Correspondence - Email T.Marshall/G.Scott - Update on Gilead's ABS NDA 22-081 Amend 019. Summary of CMC Agreements Reached During June 8, 2007 CMC Teleconference	2007-06-11_22081_CORR_EMAIL_SGOLDIE_TMA_RSHALL_1.pdf	22-081	
1	Regulatory	US	6/8/2007	Temp 6	FDA Correspondence - Phone	L.Tanner/T.Marciniak - Feedback regarding FDA comments to PI.	2007-06-08_22081_CORR_PHONE_LTANNER_TM_ARCINIAK.pdf	22-081
1	Regulatory	US	6/8/2007	Temp 6	FDA Correspondence - Email T.Marshall/G.Scott - T Con participants.	2007-06-08_22081_CORR_EMAIL_SGOLDIE_TMA_RSHALL_1.pdf	22-081	

1	Regulatory	US	6/7/2007	Temp 6	FDA Correspondence - Email D.Brum/L.Tanner - Notifications about comments on PI.	07_22081_CORR_EMAIL_LTANNER_DBR UM 2.pdf	22-081
1	Regulatory	US	6/7/2007	Temp 6	FDA Correspondence - Email L.Tanner/D.Brum. The phone calls on 06/06/07 and 06/07/07. Process and Timing for Receiving FDA Comments to PI. Process for submitting revised RiskMAP and associated Materials.	07_22081_CORR_PHONE_LTANNER_DBR UM.pdf	2007-06-22-081
1	Regulatory	US	6/7/2007	Temp 6	FDA Correspondence - Email L.Tanner/D.Brum. NDA 22-081: Tracleer Label	07_22081_CORR_EMAIL_LTANNER_DBR UM 1.pdf	2007-06-22-081
1	Regulatory	US	6/7/2007	Temp 6	FDA Correspondence - Email L.Tanner/D.Brum. NDA 22-081: Comments on Proposed RiskMAP	07_22081_CORR_EMAIL_LTANNER_DBR UM.pdf	2007-06-22-081
1	Regulatory	US	6/7/2007	Temp 6	FDA Correspondence - Email L.Tanner/M.Gordon - Subject: Processes and Timing for Receiving FDA Comments to PI. Processes for submitting revised RiskMAP and associated Materials.	07_22081_CORR_PHONE_LTANNER_DBR UM.pdf	2007-06-22-081
1	Regulatory	US	6/7/2007	Temp 6	FDA Correspondence - Email L.Tanner/M.Gordon - The phone calls to confirm that CRF pages for subject 2050/248-001resent and that there are no further outstanding issues regarding input into the PI.	07_22081_CORR_PHONE_LTANNER_DBR UM 2.pdf	2007-06-22-081
1	Regulatory	US	6/7/2007	Temp 6	FDA Correspondence - Email M.Gordon/L.Tanner - &-day report; Subject 2050/248-001 (updated forms). The CRFs forms attached.	06_22081_CORR_EMAIL_LTANNER_MG ORDON.pdf	2007-06-22-081
1	Regulatory	US	6/6/2007	Book 5	FDA Correspondence - Email M.Gordon/L.Tanner - Message email from May 29, 2007 has been lacked.	06_22081_CORR_EMAIL_LTANNER_MG ORDON.pdf	2007-06-22-081
1	Regulatory	US	6/6/2007	Book 5	FDA Correspondence - Email L.Tanner/D.Brum. NDA 22-081: Reformatted MedGuide for LETAIRIS™(ambriksentan)	06_22081_CORR_EMAIL_LTANNER_DBR UM.pdf	2007-06-22-081
1	Regulatory	US	6/5/2007	Book 5	FDA Correspondence - Email T.Marshall/G.Scott - The FDA participants - May 23, 2007 teleconference regarding NDA 22-081	05_22081_CORR_EMAIL_SGOLDIE_TMA RSHALL.pdf	2007-06-22-081
1	Regulatory	US	6/5/2007	Book 5	FDA Correspondence - Email D.Brum. Two phone calls on 06/04/07 and 06/05/0. Process for finalizing Medication Guide, PI, and RiskMAP	05_22081_CORR_PHONE_LTANNER_DBR UM.pdf	2007-06-22-081

1	Regulatory	US	6/4/2007	Book 5	FDA Correspondence - Email L.Tanner/D.Brum. RiskMAP revised proposal.	2007-06-UM.pdf	22-081
1	Regulatory	US	6/2/2007	Book 5	FDA Correspondence - Email D.Brum/L.Tanner - MedGuide and PI	2007-06-ER.pdf	22-081
1	Regulatory	US	6/1/2007	Book 5	FDA Correspondence - Email T.Marshall/S.Goldie. The response to CMC specification changes discussed during May 23, 2007 CMC teleconference. NDA 22-081 Amendment 0017 attached.	01_22081_CORR_EMAIL_SGOLDIE_TMARSHALL.pdf	22-081
1	Regulatory	US	6/1/2007	Book 5	FDA Correspondence - Email L.Tanner/D.Brum. E-mail from Dan Brum, FDA Project Manager, who has requested that Gilead resend the Medication Guide for ambisentan that "looks" like Tracleer. Attached are the Medication Guides for Tracleer and Letairis.	01_22081_CORR_EMAIL_DBRUM_LTANNER_ER_1.pdf	22-081
1	Regulatory	US	6/1/2007	Book 5	FDA Correspondence - Phone	2007-06-UM.pdf	22-081
1	Regulatory	US	6/1/2007	Book 5	FDA Correspondence - Email L.Tanner/D.Brum. Subject: Process for resolving PI Issues. FDA Minutes from 25 May 2007 Teleconference. Company Audit Details Dr.Galie.	01_22081_CORR_PHONE_LTANNER_DBRUM_LTANNER_ER.pdf	22-081
1	Regulatory	US	6/1/2007	Book 5	FDA Correspondence - Email L.Tanner/D.Brum. Email with two attachments. Subject: The Gilead details of the audit at Dr. Galie's site.	01_22081_CORR_EMAIL_DBRUM_LTANNER_ER.pdf	22-081
1	Regulatory	US	6/1/2007	Book 5	FDA Correspondence - Email D.Brum/L.Tanner. Email with the FDA Meeting Minutes from May 25, 2007.	01_22081_CORR_PHONE_LTANNER_DBRUM_LTANNER_ER_2.pdf	22-081
1	Regulatory	US	5/31/2007	Book 5	FDA Correspondence - Phone	2007-05-UM.pdf	22-081
1	Regulatory	US	5/31/2007	Book 5	FDA (DDMAC) Correspondence - Fax	31_22081_CORR_PHONE_LTANNER_DBRUM_LTANNER_ER.pdf	22-081
1	Regulatory	US	5/30/2007	Book 5	FDA Correspondence - Email L.Tanner/D.Brum. Response to FDA Comments to RiskMAP. Cover Letter (Amendment No. 16 to NDA 22-081) attached.	30_22081_CORR_EMAIL_DDMAC_FAX.pdf	22-081

1	Regulatory	US	5/25/2007	Book 5	FDA Correspondence - Email L.Tanner/M.Gordon. 7 day report; CRF 248-001-2020	2007-05-22-081
1	Regulatory	US	5/24/2007	Book 5	FDA Correspondence - Email L.Tanner/D.Brum. Confirm Teleconference Time (2:30 EDT) and addition of Jennifer Stewart as a Participant.	2007-05-22-081
1	Regulatory	US	5/24/2007	Book 5	FDA Correspondence - Email L.Tanner/D.Brum. Acceptability of Revised Labeling (Primary and Secondary Packaging). NDA 22-081.	2007-05-22-081
1	Regulatory	US	5/24/2007	Book 5	FDA Correspondence - Email L.Tanner/D.Brum. RiskMAP Questions	2007-05-22-081
1	Regulatory	US	5/24/2007	Book 5	FDA Correspondence - Email L.Tanner/D.Brum. FDA comments to Packaging	2007-05-22-081
1	Regulatory	US	5/23/2007	Book 5	FDA Correspondence - Email T.Marshall/S.Goldie. Ambrisentan Registration Tablets Dissolutions Data.	2007-05-22-081
1	Regulatory	US	5/22/2007	Book 5	FDA Correspondence - Email L.Tanner/D.Brum. Confirmation of Participants and Call-in Number for FDA-Gilead Teleconference 05/25/2007.	2007-05-22-081
1	Regulatory	US	5/21/2007	Book 5	FDA Correspondence - Email L.Tanner/D.Brum. Clarification for Processes in Reviewing the RiskMAP, Including attachment of Meeting Minutes from March 29, 2007 teleconference with FDA.	2007-05-22-081
1	Regulatory	US	5/17/2007	Book 5	FDA Correspondence - Email L.Tanner/D.Brum. Acceptability of Revised Labeling (Primary and Secondary Packaging). NDA 22-081.	2007-05-22-081
1	Regulatory	US	5/14/2007	Book 5	FDA Correspondence - Letter E.Fromm/L.Tanner. Discipline Review Letter. The comments on the RiskMAP portion of NDA 22-081 from the Office of Surveillance and Epidemiology.	2007-05-22-081
1	Regulatory	US			T.Marshall/S.Goldie (Calles made on 4/30/07, 05/02/07, 05/03/07, 05/08/07, 05/14/07) - CMC Information Request, NDA Amendment 13: Updating List of Establishments and Pre-Approval Inspections. NDA 22-081.	2007-05-22-081

1	Regulatory	US	5/11/2007	Book 5	FDA Correspondence - Letter L.Tanner/D.Brum. Desk Copies. 022081 - Amendment No. 14. Briefing Document for 25 May 2007	2007-05-14_22081_CORR_EMAIL_DBRUM_LTANN ER.pdf	22-081	
1	Regulatory	US	5/9/2007	Book 5	FDA Correspondence - Email T.Marshall/S.Goldie - Response to the 8 comments/questions letter from 04/30/2007 . NDA 22-081	2007-05-09_22081_CORR_EMAIL_SGOLDIE_TMA RSHALL.pdf	22-081	
1	Regulatory	US	5/7/2007	Book 5	FDA Correspondence - Phone	L.Tanner/M.Robb. Three calls on 5/03/07, 5/04/07 and 05/07/07 - Subject: Processing during labeling	2007-05-07_22081_CORR_PHONE_LTANNER_MR OBB.pdf	22-081
1	Regulatory	US	5/7/2007	Book 5	FDA Correspondence - Email L.Tanner/M.Robb - Subject: FedEx Shipment Notification from M.Robb (FDA).	07_22081_CORR_PHONE_LTANNER_MR OBB.pdf	2007-05-07_22081_CORR_EMAIL_LTANNER_MRO BB.pdf	22-081
1	Regulatory	US	5/4/2007	Temp 7	FDA (DDMAC) Submission NDA 22-081	DDMAC Promotional Materials for NDA 22-081. Request for Perspective Review and Advisory Comments for Product Launch Materials for NDA 22-081 Lataris™ (ambrisentan 5 mg and 10 mg tablets) GSI Ref. No.000.	2007-05-04_22081_CORR_DDMAC_PROMO_MATE RIALS.pdf	22-081
1	Regulatory	US	5/3/2007	Book 4	FDA Correspondence - Email L.Tanner/M.Robb - Subject: Response to DMETS, including revised labeling.	03_22081_CORR_EMAIL_LTANNER_MRO BB.pdf	2007-05-03_22081_CORR_EMAIL_LTANNER_MRO BB.pdf	22-081
1	Regulatory	US	5/1/2007	Book 4	FDA Correspondence - Email L.Tanner/M.Gordon - Subject: Response to Clinical Questions. NDA 22-081	01_22081_CORR_EMAIL_LTANNER_MG ORDON.pdf	2007-05-01_22081_CORR_EMAIL_LTANNER_MG ORDON.pdf	22-081
1	Regulatory	US	4/30/2007	Book 4	FDA Correspondence - Email L.Tanner/M.Robb - Subject: Updated PI Incorporating DMETS Recommendations (Version 1).	01_22081_CORR_EMAIL_LTANNER_MG BB.pdf	2007-05-01_22081_CORR_EMAIL_LTANNER_MG BB.pdf	22-081
1	Regulatory	US	4/30/2007	Book 4	FDA Correspondence - Letter R.Sood/T.Marshall. Information request letter from FDA (review and comments of CMC section for NDA 22-081).	30_22081_CORR LETTER_RSOOD_TMAR SHALL.pdf	2007-04-30_22081_CORR LETTER_RSOOD_TMAR SHALL.pdf	22-081
1	Regulatory	US	4/30/2007	Book 4	FDA Correspondence - Phone	L.Tanner/M.Robb. Two phone calls on 4/27/07 and 4/30/07. Subject: Briefing document for May 25 teleconference to discuss proposal to measure 6MWD at trough and peak. NDA 22-081.	2007-04-30_22081_CORR_PHONE_LTANNER_MR OBB.pdf	22-081
1	Regulatory	US	4/30/2007	Book 4	FDA Correspondence - Fax	S.Goldie/T.Marshall. Information Request Letter included. NDA 22-081.	2007-04-30_22081_CORR_FAX_SGOLDIE_TMARS HALL.pdf	22-081

1	Regulatory	US	4/26/2007	Book 4	FDA Correspondence - Phone	L. Tanner/M.Robb - Three phone calls on 4/20/07, 4/24/07, 4/26/07. Subject: Plan Promotional Materials; DMETS Comments; Process Labeling Revisions NDA 22-081	2007-04-22-081
1	Regulatory	US	4/26/2007	Book 4	FDA Correspondence - Email	L.Tanner/M.Robb - Subject: Proposed plan for submitting promotional materials for use with the first 120 days post-approval.. NDA 22-081	2007-04-22-081
1	Regulatory	US	4/24/2007	Book 4	FDA Correspondence - Email	L.Tanner/M.Robb - Regarding proposed plan for submitting promotional materials for use with the first 120 days post-approval.. NDA 22-081	2007-04-22-081
1	Regulatory	US	4/23/2007	Book 4	FDA Correspondence - Letter	E.Fromm/L.Tanner -Discipline Review Letter from FDA, Office of Surveillance and Epidemiology's DMETS. NDA 22-081	2007-04-22-081
1	Regulatory	US	4/23/2007	Book 4	FDA Correspondence - Email	L.Tanner/M.Robb - Response regarding randomization. NDA 22-081	2007-04-22-081
1	Regulatory	US	4/19/2007	Book 4	FDA Correspondence - Email	L.Tanner/P.Hinderling - Response to Questions Regarding Bioanalytical Assay Issues; NDA 22-081	2007-04-19_22081_CORR_EMAIL_LTANNER_MM.pdf
1	Regulatory	US	4/19/2007	Book 4	FDA Correspondence - Email	L.Tanner/P.Hinderling - Response to additional request Multimedia Dissolution Profiles; NDA 22-081	2007-04-19_22081_CORR_EMAIL_LTANNER_MM.pdf
1	Regulatory	US	4/19/2007	Book 4	FDA Correspondence - Email	L.Tanner/M.Robb - NDA 22-08; Follow-up information to Clinical Review Question 4 from e-mail dated 09 March 2007.	2007-04-19_22081_CORR_EMAIL_LTANNER_MM.pdf
1	Regulatory	US	4/17/2007	Book 4	FDA Correspondence - Phone	T.Marshall/S.Goldie - Three phone calls on 04/09/07, 04/16/07 and 04/17/07 Subject: Proposed "CMC" Amendment to Ambrisentan NDA to revise listed establishments/functions and to provide corrections to typos/minor errors. NDA 22-081	2007-04-17_22081_CORR_PHONE_TMARSHALL_S_GOLDIE.pdf
1	Regulatory	US	4/17/2007	Book 4	FDA Correspondence - Email	L.Tanner/M.Robb - Request for Meeting to discuss Dosing Interval; Follow-up to March 29 Meeting. NDA 22-081	2007-04-17_22081_CORR_EMAIL_LTANNER_MM.pdf

1	Regulatory	US	4/16/2007	Book 4	FDA Correspondence - Fax	M.Robb/L.Tanner - The FDA Teleconference Meeting Minutes (March 29, 2007). NDA 22-081.	2007-04-16_22081_CORR_FAX_LTANNER_MRROBB_MEETING_MINUTES.pdf	22-081
1	Regulatory	US	4/16/2007	Book 4	FDA Correspondence - Email L.Tanner/P.Hinderling - Follow-up email to request validation dilution.	L.Tanner/P.Hinderling - Follow-up email to request validation dilution.	16_22081_CORR_EMAIL_LTANNER_PHI_NDERLING.pdf	22-081
1	Regulatory	US	4/16/2007	Book 4	FDA Correspondence - Phone	L.Tanner/M.Robb - Confirm the date and time for teleconference (Amendment to AMB-323). Confirm name of new Project Manager. NDA 22-081	2007-04-16_22081_CORR_PHONE_LTANNER_MR_OBB.pdf	22-081
1	Regulatory	US	4/16/2007	Book 4	FDA Correspondence - Email L.Tanner/P.Hinderling - Response to Questions Regarding Dissolution Profiles; NDA 22-081	L.Tanner/M.Robb - Response to Questions Regarding Dissolution Profiles; NDA 22-081	16_22081_CORR_EMAIL_LTANNER_PHI_NDERLING_1.pdf	22-081
1	Regulatory	US	4/13/2007	Book 4	FDA Correspondence - Email L.Tanner/M.Robb - Request for Teleconference: Advice Clinical Inspection.	L.Tanner/M.Robb - Request for Teleconference: Advice Clinical Inspection.	13_22081_CORR_EMAIL_LTANNER_MRO_BB.pdf	22-081
1	Regulatory	US	4/13/2007	Book 4	FDA Correspondence - Phone	L.Tanner/M.Robb - Phone calls on 04/12/07 and 04/13/07 - Clinical Inspection for Site #207 (Nazzareno	13_22081_CORR_PHONE_LTANNER_MR_OBB.pdf	22-081
1	Regulatory	US	4/12/2007	Book 4	FDA Correspondence - Email L.Tanner/M.Robb - Email to M. Robb indicating that Gilead acknowledged and understood the Clinical Pharmacology issues that P. Hinderling addressed in his written comments (03/29/07 - FDA teleconference). NDA 22-081	L.Tanner/M.Robb - Email to M. Robb indicating that Gilead acknowledged and understood the Clinical Pharmacology issues that P. Hinderling addressed in his written comments (03/29/07 - FDA teleconference). NDA 22-081	12_22081_CORR_EMAIL_LTANNER_MRO_BB.pdf	22-081
1	Regulatory	US	4/12/2007	Book 4	FDA Correspondence - Email L.Tanner/P.Hinderling - Response to Questions Regarding Dissolution Profiles; NDA 22-081	L.Tanner/P.Hinderling - Response to Questions Regarding Dissolution Profiles; NDA 22-081	12_22081_CORR_EMAIL_LTANNER_PHI_NDERLING.pdf	22-081
1	Regulatory	US	4/9/2007	Book 4	FDA Correspondence - Phone	L.Tanner/M.Robb. Subject: Status of scheduling teleconference regarding plan to support once-daily dosing. Submission of promotional materials.	09_22081_CORR_PHONE_LTANNER_MR_OBB.pdf	22-081
1	Regulatory	US	4/5/2007	Book 4	FDA Correspondence - Email L.Tanner/P.Hinderling - Request from P. Hinderling requesting F2 tests of respective dissolution profiles are various pHs for clinical and commercial products.	F2 tests of respective dissolution profiles are various pHs for clinical and commercial products.	05_22081_CORR_EMAIL_LTANNER_PHI_NDERLING.pdf	22-081

1	Regulatory	US	4/4/2007	Book 4	FDA Correspondence - Phone	L.Curran/V.Ventura - Clarification of submission format. NDA 22-081	04_22081_CORR_PHONE_LCURRAN_VVE_NTURA.pdf	22-081
1	Regulatory	US	4/3/2007	Book 4	FDA Correspondence - Email	L.Tanner/M.Robb - Request for Meeting to discuss Dosing Interval; Followup to March 29 Meeting. NDA 22-081	03_22081_CORR_EMAIL_LTANNER_MRO_BB.pdf	22-081
1	Regulatory	US	3/28/2007	Book 3	FDA Correspondence - Phone	L.Tanner/M.Robb. Three phone calls on 03/26/07, 03/27/07 and 03/28/07. Subjects: Preparation for March 29, 2007 90-Day Teleconference (NDA review status). Amendment No.8. Issues with e-mails sent to Melissa Robb. NDA 22-081.	28_22081_CORR_PHONE_LTANNER_MR_OBB.pdf	22-081
1	Regulatory	US	3/28/2007	Book 3	FDA Correspondence - Email	L.Tanner/M.Robb - Summary of Amendments submitted or will be submitted to NDA 22-081.	28_22081_CORR_EMAIL_LTANNER_MRO_BB_1.pdf	22-081
1	Regulatory	US	3/28/2007	Book 3	FDA Correspondence - Email	L.Tanner/M.Robb - Plan for submitting electronic datasets are acceptable.	28_22081_CORR_EMAIL_LTANNER_MRO_BB_1.pdf	22-081
1	Regulatory	US	3/27/2007	Book 3	FDA Correspondence - Fax	L.Tanner/M.Robb - Pre-Meeting Comments NDA 22-081	27_22081_CORR_FAX_LTANNER_MROBB.pdf	22-081
1	Regulatory	US	3/27/2007	Book 3	FDA Correspondence - Email	L.Tanner/M.Robb - Revised List of Gilead Participants and Call-in Number. NDA 22-081	27_22081_CORR_EMAIL_LTANNER_MRO_BB_2.pdf	22-081
1	Regulatory	US	3/27/2007	Book 3	FDA Correspondence - Email	L.Tanner/M.Robb - List of Gilead Participants and Call-in Number. NDA 22-081	27_22081_CORR_EMAIL_LTANNER_MRO_BB.pdf	22-081
1	Regulatory	US	3/26/2007	Book 3	FDA Correspondence - Email	L.Tanner/M.Robb - Response to questions in e-mail dated 9/03/07; Amendment No. 8, NDA 22-081	26_22081_CORR_EMAIL_LTANNER_MRO_BB_1.pdf	22-081
1	Regulatory	US	3/26/2007	Book 3	FDA Correspondence - Email	L.Tanner/M.Robb - Word questions submitted in meeting request (Amendment No.5). NDA 22-081	26_22081_CORR_EMAIL_LTANNER_MRO_BB.pdf	22-081
1	Regulatory	US	3/22/2007	Book 3	FDA Correspondence - Phone	M.Plamondon/E.Smith - Mr. Smith was following up on Gilead Colorado's registration as a manufacturer.	22_22081_CORR_PHONE_MPLAMONDON_ESMITH.pdf	22-081

1	Regulatory	US	3/20/2007	Book 3	FDA Correspondence - Phone	L. Tanner/S.Gershon - FDA Inspection for Site # 207 (Nazzareno Galie) Italy. NDA 22-081	2007-03- RSHON.pdf	22-081
1	Regulatory	US	3/20/2007	Book 3	FDA Correspondence - Email	L. Tanner/M.Robb - Gilead Response to FDA regarding the request for Efficacy and Safety Datasets AMB-220, AMB-222, PK/PD PopPK. NDA 22-081	2007-03- BB.pdf	22-081
1	Regulatory	US	3/19/2007	Book 3	FDA Correspondence - Email	L. Tanner/M.Robb - Request for Efficacy and Safety Datasets AMB-220, AMB-222, PK/PD PopPK. NDA 22-081	19_22081_CORR_EMAIL_LTANNER_MRO BB.pdf	22-081
1	Regulatory	US	3/13/2007	Book 3	FDA Correspondence - Email	L. Tanner/M.Robb - The PDF file of Amendment No. 6. NDA 22-081.	13_22081_CORR_EMAIL_LTANNER_MRO BB.pdf	22-081
1	Regulatory	US	3/13/2007	Book 3	FDA Correspondence - Phone	L. Tanner/M.Robb (Phone calls on 03/05/07, 03/06/07, 03/08/07& 03/13/07) - Status feedback Letairis; Meeting request. NDA 22-081	13_22081_CORR_PHONE_LTANNER_MR OBB.pdf	22-081
1	Regulatory	US	3/9/2007	Book 3	FDA Correspondence - Phone	L. Tanner/S.Gershon - The official contact report with Sharon Gershon regarding the status of the inspection of Dr. Galie (Italy)	09_22081_CORR_EMAIL_LTANNER_SGE RSHON.pdf	22-081
1	Regulatory	US	3/9/2007	Book 3	FDA Correspondence - Email	L. Tanner/P.Hinderling - Formatting Changes and Instructions for PI. NDA 22-081	09_22081_CORR_EMAIL_LTANNER_PHI NDERLING.pdf	22-081
1	Regulatory	US	3/9/2007	Book 3	FDA Correspondence - Email	L. Tanner/M.Robb - Ambrisentan Questions. NDA 22-081.	09_22081_CORR_EMAIL_MROBB_LTANN ER.pdf	22-081
1	Regulatory	US	3/8/2007	Book 3	FDA Correspondence - Email	L. Tanner/M.Robb - The e-mail sent to Melissa Robb inquiring about the status of the proprietary name of LETAIRIS. (Note: This question was answered in a teleconference report dated 3-13-07 to Melissa Robb). NDA 22-081	2007-03- BB.pdf	22-081
1	Regulatory	US	3/8/2007	Book 3	FDA Correspondence - Email	L. Tanner/P.Hinderling - Formatting Changes and Instructions for PI. NDA 22-081	08_22081_CORR_EMAIL_LTANNER_PHI NDERLING.pdf	22-081
1	Regulatory	US	3/8/2007	Book 3	FDA Correspondence - Fax	M.Robb/L.Tanner - Teleconference meeting conformation - March 29, 2007. NDA 22-081.	08_22081_CORR_FAX_MROBB_LTANNER .pdf	22-081

1	Regulatory	US	3/7/2007	Book 3	FDA Correspondence - Email L. Tanner/P.Hinderling - Unformatted PI for Ambrisentan; NDA 22-081; Option to resolve formatting PI.	2007-03-07_22081_CORR_EMAIL_LTANNER_PHI_NDERLING.pdf	22-081
1	Regulatory	US	3/6/2007	Book 3	FDA Correspondence - Email L. Tanner/M.Gordon - Formal Response on Clinically Significant Abnormal ECGs. NDA 22-081.	2007-03-06_22081_CORR_EMAIL_LTANNER_MG_ORDON.pdf	22-081
1	Regulatory	US	3/6/2007	Book 3	FDA Correspondence - Email L. Tanner/M.Robb - Unformatted PI for Ambrisentan - No need to submit to the NDA. 22-081.	2007-03-06_22081_CORR_EMAIL_LTANNER_MRO_BB.pdf	22-081
1	Regulatory	US	3/5/2007	Book 3	FDA Correspondence - Email L. Tanner/M.Robb/P.Hinderling - Unformatted PI for Ambrisentan; NDA 22-081.	2007-03-05_22081_CORR_EMAIL_LTANNER_MRO_BB.pdf	22-081
1	Regulatory	US	3/3/2007	Book 3	FDA Correspondence - Email L. Tanner/M.Robb - request for the meeting to discuss status of review of NDA 22-081. Update on Amendments submitted to NDA. Amendment 5 attached.	2007-03-03_22081_CORR_EMAIL_LTANNER_MRO_BB.pdf	22-081
1	Regulatory	US	3/2/2007	Book 3	FDA Correspondence - Phone	2007-03-02_22081_CORR_PHONE_LTANNER_PHI_NDERLING.pdf	22-081
1	Regulatory	US	2/27/2007	Book 2	FDA Correspondence - Email L. Tanner/M.Gordon - The initial response regarding clinically significant abnormal ECGs which was submitted to Mary Gordon on 02/27/07. NDA 22-081	2007-02-27_22081_CORR_EMAIL_LTANNER_MG_ORDON.pdf	22-081
1	Regulatory	US	2/22/2007	Book 2	FDA Correspondence - CD-ROM	2007-02-21_22081_CORR_PHONE_LTANNER_MR_OBB.pdf	22-081
1	Regulatory	US	2/21/2007	Book 2	FDA Correspondence - Phone	2007-02-21_22081_CORR_PHONE_LTANNER_MR_OBB.pdf	22-081
1	Regulatory	US	2/21/2007	Book 2	FDA Correspondence - Email L. Tanner/M.Gordon. The FDA e-mail contact report that provides the plan to provide Maryann Gordon the CRFs that were not previously submitted for subjects who discontinued from Phase 1 studies. NDA 22-081.	2007-02-21_22081_CORR_EMAIL_LTANNER_MG_ORDON.pdf	22-081

1	Regulatory	US	2/20/2007	Book 2	FDA Correspondence - Email The E-mail with Maryann Gordon regarding our intention to provide the CRF for Subject 38 in Study EE-001. NDA 22-081	20_22081_CORR_EMAIL_LTANNER_MG_ORDON.pdf	22-081
1	Regulatory	US	2/16/2007	Book 2	FDA Correspondence - Letter N.Stockbridge/M.Gerber - Filling Communication. Filling accepted and priority filling granted. NDA 22-081.	16_22081_CORR LETTER_NSTOCKBRID GE_MGERBER.pdf	22-081
1	Regulatory	US	2/16/2007	Book 2	FDA Correspondence - Phone	L.Tanner/M.Robb - Phone on 02/13/07, 02/14/07, 02/16/07 to confirm status of NDA filing letter and process for formally submitting responses that have already been emailed to reviewers. NDA 22-081	2007-02-081_CORR_PHONE_LTANNER_MR_OBB.pdf
1	Regulatory	US	2/16/2007	Book 2	FDA Correspondence - Email L.Tanner/M.Robb - RE: NDA 22-081; Status of Feedback Regarding Acceptability of Trade name LETAIRIS (Amendment No. 1)	16_22081_CORR_EMAIL_MROBB_LTANNER_ER.pdf	22-081
1	Regulatory	US	2/16/2007	Book 2	FDA Correspondence - Email L.Tanner/M.Robb - E-mail response to Melissa Robb regarding how refills would be handled in the RiskMAP.	16_22081_CORR_EMAIL_LTANNER_MRO_BB.pdf	22-081
1	Regulatory	US	2/15/2007	Book 2	FDA Correspondence - Email L.Tanner/P.Hinderling - Summary of PT and INR Methodology. Protim Summary Information doc. Attached.	15_22081_CORR_EMAIL_LTANNER_PHI_NDERLING.pdf	22-081
1	Regulatory	US	2/14/2007	Book 2	FDA Correspondence - Phone	Phone - Nikolas Burlew (Regulus Pharmaceutical) called Nancy Schmidt (FDA-Denver District) to establish registration for Gilead Colorado.	2007-02-14_22081_CORR_PHONE_NBURLEW_NSCH_MIDT.pdf
1	Regulatory	US	2/14/2007	Book 2	FDA Correspondence - Email M.Robb/L.Tanner/ - Email from M. Robb with additional question.(Ambrisentan and RiskMAP). NDA 22-081	14_22081_CORR_EMAIL_LTANNER_MRO_BB.pdf	22-081
1	Regulatory	US	2/14/2007	Book 2	FDA Correspondence - Email L.Tanner/P.Hinderling - Email indicating that Gilead is continuing to work with our vendor to obtain the PT and INR methodology for AMB-106. NDA 22-081	14_22081_CORR_EMAIL_LTANNER_PHI_NDERLING.pdf	22-081
1	Regulatory	US	2/13/2007	Book 2	FDA Correspondence - Phone	L.Tanner/M.Robb - Confirm for handling requests directly from reviewer. E-mail dated 2/13/07 regarding RiskMAP and distribution. Filling Letter.	2007-02-081_CORR_PHONE_LTANNER_MR_OBB.pdf

1	Regulatory	US	2/13/2007	Book 2	FDA Correspondence - Email L.Tanner/M.Robb - Gilead response to the questions from FDA on the distribution of Ambisentan and RiskMAP. The patient enrollment form attached. NDA 22-081	2007-02-13_22081_CORR_EMAIL_LTANNER_MRO_BB.pdf	22-081	
1	Regulatory	US	2/12/2007	Book 2	FDA Correspondence - Phone	M.Gordon/H.Isozski. Maryann Gordon called and request to talk to L. Tanner. NDA 22-081	2007-02-12_22081_CORR_PHONE_MGORDON_HIS_OKOSKI.pdf	22-081
1	Regulatory	US	2/12/2007	Book 2	FDA Correspondence - Email	M.Gordon/L.Tanner - Another E-mail from Maryann Gordon asking that we submit all clinical information sent to her formally to the NDA.	2007-02-12_22081_CORR_EMAIL_LTANNER.pdf	22-081
1	Regulatory	US	2/12/2007	Book 2	FDA Correspondence - Email	M.Gordon/L.Tanner - E-mail contact report with Maryann Gordon regarding regenerating a table for LFTs from AMB-222 for archival in the database.	2007-02-12_22081_CORR_EMAIL_LTANNER_MG_ORDON.pdf	22-081
1	Regulatory	US	2/12/2007	Book 2	FDA Correspondence - Email	L.Tanner/M.Robb - FDA questions on the distribution of Ambrisentan and RiskMAP.	2007-02-12_22081_CORR_EMAIL_LTANNER_MRO_BB.pdf	22-081
1	Regulatory	US	2/9/2007	Book 2	FDA Correspondence - Phone	L.Tanner/M.Gordon - Confirm the requirements for clinical information requested in emails dated 02/07/07 & 02/09/07.	2007-02-09_22081_CORR_PHONE_LTANNER_MG_ORDON.pdf	22-081
1	Regulatory	US	2/9/2007	Book 2	FDA Correspondence - Email	L.Tanner/M.Gordon - email sent to M.Gordon regarding her request for additional clinical information. The email contains all of the attachments. NDA 22-081.	2007-02-09_22081_CORR_EMAIL_LTANNER_MG_ORDON.pdf	22-081
1	Regulatory	US	2/9/2007	Book 2	FDA Correspondence - Email	E-mail from Peter Hinderling conforming that he received the replacement pages for EE-002	2007-02-09_22081_CORR_EMAIL_LTANNER_PHI_HINDERLING.pdf	22-081
1	Regulatory	US	2/8/2007	Book 2	FDA Correspondence - Email	E-mail that was submitted to Peter Hinderling, Clinical Pharmacology Reviewer, which contains the replacement pages with figures that are easier to read from EE-002 at his request.	2007-02-08_22081_CORR_EMAIL_LTANNER_PHI_HINDERLING.pdf	22-081
1	Regulatory	US	2/8/2007	Book 2	FDA Correspondence - Email	L.Tanner/M.Gordon - Conformation of Teleconference on Friday, February 9, 10:00 a.m. EST	2007-02-08_22081_CORR_EMAIL_LTANNER_MG_ORDON.pdf	22-081

1	Regulatory	US	2/8/2007	Book 2	FDA Correspondence - Phone	M.Gordon/L.Tanner - Schedule time for teleconference to discuss process for capturing lab values.	08_22081_CORR_PHONE_MGORDON_LTANNER.pdf	22-081
1	Regulatory	US	2/6/2007	Book 2	FDA Correspondence - Phone	H.Isokoski/P.Hinderling - The Methodology to determine Prothrombin Time (PT) and International Normalized Ratio (INR) in AMB-106 and Legible Figures for the report EE-002.	06_22081_CORR_PHONE_PHINDERLING_HISOKOSKI.pdf	22-081
1	Regulatory	US	2/5/2007	Book 2	FDA Correspondence - Email L.Tanner/M.Robb - E-mail correspondence; Request for Location QTc documentation, Clinical Pharmacology Summary Table. The FDA Response, 2006 Clin. Final IB and FDA Notification App. Attached.	05_22081_CORR_EMAIL_LTANNER_MRO_BB.pdf		22-081
1	Regulatory	US	2/2/2007	Book 1	FDA Correspondence - Email L.Tanner/S.Gershon - Confirm that CD's were sent with information for Clinical Inspections. Attached to the email is the cover letter.	02_22081_CORR_EMAIL_LTANNER_SGE_RSHON.pdf		22-081
1	Regulatory	US	2/2/2007	Book 1	FDA Correspondence - Phone	L.Tanner/M.Gordon - Confirm that Maryann Gordon was able to retrieve the CRF for Subject 109-002.	02_22081_CORR_PHONE_MGORDON_LTANNER.pdf	22-081
1	Regulatory	US	2/2/2007	Book 1	FDA Correspondence - CD-ROM	Desk Copy Request for Site Specific Information. NDA 22-081	Clinical_Inspection_Request-Desk_Copy	22-081
1	Regulatory	US	2/1/2007	Book 1	FDA Correspondence - Phone	E.Smith/L.Tanner & M.Plamondon - E.Smith of the Denver District Office of the FDA called regarding the ambrisentan NDA.	01_22081_CORR_PHONE_ESMITH_LTANNER_MPLAMONDON.pdf	22-081
1	Regulatory	US	2/1/2007	Book 1	FDA Correspondence - Phone	L.Tanner/M.Gordon - Clarity whether CRF for Subject 109-002 was submitted in NDA	01_22081_CORR_PHONE_LTANNER_MGORDON.pdf	22-081
1	Regulatory	US	2/1/2007	Book 1	FDA Correspondence - Email S.Gershon/L.Tanner - Conform Information to be provided on CD's; Clinical Inspections NDA 22-081.	01_22081_CORR_EMAIL_SGERSHON_LTANNER.pdf		22-081
1	Regulatory	US	1/31/2007	Book 1	FDA Correspondence - Email L.Tanner/M.Robb - Conformation that CRFs for subject 156-007 and 126-008 was received at FDA.	31_22081_CORR_EMAIL_LTANNER_MRO_BB_156-007.pdf		22-081

1	Regulatory	US	1/30/2007	Book 1	FDA Correspondence - Phone	L. Tanner/S.Gershon - Confirm acceptability of listings that will be included in the information package on the CDs that will be submitted to her for use during the FDA clinical inspections.	2007-01- RSHON.pdf	22-081
1	Regulatory	US	1/30/2007	Book 1	FDA Correspondence - Phone	L. Tanner/M.Robb - Confirm that Amendment #2 was received at FDA on January 30, 2007. NDA 22-081.	2007-01- OBB_156-007.pdf	22-081
1	Regulatory	US	1/30/2007	Book 1	FDA Correspondence - Phone	L. Tanner/M.Gordon - Death of female subject (221-003) enrolled in the extension study (AMB-32/321-3). NDA 22-081	2007-01- ORDON.pdf	22-081
1	Regulatory	US	1/26/2007	Book 1	FDA Correspondence - Email	L. Tanner/M.Robb - CRF for Subject 156-007 requested by Dr. Marciniaik; NDA 22-081. (156-007.zip attached)	2007-01- BB_156-007.pdf	22-081
1	Regulatory	US	1/26/2007	Book 1	FDA Correspondence - Email	L. Tanner/M.Robb - CRF for subject 126-008 requested by Dr. Marciniaik; NDA 22-081. (126-008.zip attached)	2007-01- BB_126-008.pdf	22-081
1	Regulatory	US	1/26/2007	Book 1	FDA Correspondence - Email	L. Tanner/S.Gershon - Confirm information to be provided on CD's; Clinical Inspections NDA 22-081	2007-01- RSHON.pdf	22-081
1	Regulatory	US	1/25/2007	Book 1	FDA Correspondence - Phone	L. Tanner/S.Gershon - Reminder for non-USA contact information for Site #207 (Nazzareno Galie, Italy) NDA 22-08.	2007-01- RSHON.pdf	22-081
1	Regulatory	US	1/25/2007	Book 1	FDA Correspondence - Email	L. Tanner/S.Gershon - Contact Information Italian Inspector; NDA 22-081 (ambrisentan)	2007-01- RSHON.pdf	22-081
1	Regulatory	US	1/25/2007	Book 1	FDA Correspondence - Email	S.Gershon/ L.Tanner - Contact Person in Italy.	2007-01- ANNER_.pdf	22-081
1	Regulatory	US	1/23/2007	Book 1	FDA Correspondence - Email	M.Robb/L.Tanner - Email - Response from FDA to the letter dated 1/11/07. Re: Submission of complete CRFs; NDA 022-081.	2007-01- ER_.pdf	22-081
1	Regulatory	US	1/22/2007	Book 1	FDA Correspondence - Email	S.Gershon/L.Tanner - Email regarding Revised Protocol Document - Presence of Sponsors Clinical Investigations.	2007-01- ANNER_.pdf	22-081

1	Regulatory	US	1/19/2007	Book 1	FDA Correspondence - Phone S.Gershon/L.Tanner - Phone regarding FDA inspections at clinical sites that conducted Phase 3 studies AMB-320 or AMB-321.	2007-01-19_22081_CORR_PHONE_SGERSHON_LTANNER_.pdf	22-081
1	Regulatory	US	1/19/2007	Book 1	FDA Correspondence - Email L.Tanner/S.Gershon. Email regarding revised protocol documents. AMB-321 & AMB 320 protocols attached.	2007-01-19_22081_CORR_EMAIL_LTANNER_SGERSHON.pdf	22-081
1	Regulatory	US	1/19/2007	Book 1	FDA Correspondence - Email S.Gershon/ L.Tanner - Email regarding NDA 22-081 Letaris. Respond from CDER about DS1 inspections.	2007-01-19_22081_CORR_EMAIL_SGERSHON_LTANNER_.pdf	22-081
1	Regulatory	US	1/18/2007	Book 1	FDA Correspondence - Email L.Tanner/M.Robb - Response to FDA Letter Dated 1/11/07 Re: Submission of Complete CRFs, NDA 022-081	2007-01-18_22081_CORR_EMAIL_MROBB_LTANNER_.pdf	22-081
1	Regulatory	US	1/16/2007	Book 1	FDA Correspondence - Phone L.Tanner/M.Robb - Follow-up on response to Division regarding re-submission of CRFs and filing process.	2007-01-16_22081_CORR_PHONE_MROBB_LTANNER_.pdf	22-081
1	Regulatory	US	1/16/2007	Book 1	FDA Correspondence - Email L.Tanner/M.Robb - Clarification on the requested presented during the teleconference on 1/9/07. The Response to Division regarding re-submission of CRFs and filing	2007-01-16_22081_CORR_EMAIL_MROBB_LTANNER_.pdf	22-081
1	Regulatory	US	1/11/2007	Book 1	FDA Correspondence - Letter from E.Fromm/M.Gerber. Discipline Review Letter - CRFs Forms in the NDA 20-081	2007-01-11_22081_CORR LETTER_EFROOM_MGERBER.pdf	22-081
1	Regulatory	US	1/11/2007	Book 1	FDA Correspondence - Email from M. Robb to H.Isovski with the discipline review letter from FDA.	2007-01-11_22081_CORR_EMAIL_MROBB_HISOKOSKI_1.pdf	22-081
1	Regulatory	US	1/11/2007	Book 1	FDA Correspondence - Email H.Isovski/M.Robb - Email. Clarification on the requested, presented during the teleconference on 01/09/07.	2007-01-11_22081_CORR_EMAIL_MROBB_HISOKOSKI_.pdf	22-081
1	Regulatory	US	1/11/2007	Book 1	FDA Correspondence - Phone H.Isovski/M.Robb - Three phone calls. Clarification on the teleconference held on 01/09/07.	2007-01-11_22081_CORR_PHONE_HISOKOSKI_MROBB.pdf	22-081
1	Regulatory	US	1/10/2007	Book 1	FDA Correspondence - Letter E.Fromm/L.Tanner - FDA letter that acknowledges that the date of receipt of NDA 22-081 was December 18, 2006. The official filing data will be February 16, 2007	2007-01-10_22081_CORR LETTER_EFROOM_LTANNER_.pdf	22-081

1	Regulatory	US	1/9/2007	Book 1	FDA Correspondence - Phone	Gilead Teleconference Meeting Minutes with FDA - T. Marcinak.	2007-01-09_22081_CORR_PHONE_MEETING_MINUTES_TMARCINIAK_HISOKOSKI.pdf	22-081
1	Regulatory	US	1/5/2007	Book 1	FDA Correspondence - Email	Confirmation of teleconference scheduled for Tuesday, January 9, 2007 with the FDA.	2007-01-05_22081_CORR_EMAIL_MROBB_LTANN_ER.pdf	22-081
1	Regulatory	US	1/19/2007	Book 1	FDA Correspondence - Phone	L. Tanner/M. Robb - Phone No. 300-435-2000. Note that staff will not be available to participate in a teleconference with the FDA on January 19, 2007.	2007-01-05_22081_CORR_PHONE_MROBB_LTANN_ER.pdf	22-081
1	Regulatory	US	12/19/2006	Book 1	FDA Correspondence - Phone	L. Tanner/M. Robb - Feedback from M. Robb regarding the process for responding to the Division of DMETS regarding the acceptability of LETAIRIS. Attached FDA contact report from 12/18/2006 per L. Tanner.	2006-12-19_22081_CORR_PHONE_MROBB_LTANN_ER.pdf	22-081
1	Regulatory	US	12/19/2006	Book 1	FDA Correspondence - Email	L. Tanner/M. Robb - Confirmation from M. Robb that the submission NDA 22-081 was received at document room.	2006-12-19_22081_CORR_EMAIL_MROBB_LTANN_ER.pdf	22-081
1	Regulatory	US	12/18/2006	Book 1	FDA Correspondence - Email	L. Tanner/M. Robb - Confirmation that NDA 22-081 was received at FDA Mail Room.	2006-12-18_22081_CORR_EMAIL_MROBB_LTANN_ER.pdf	22-081

EXHIBIT

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U.S. PATENT NO. 5,703,017

CALCULATION OF LENGTH OF PATENT TERM EXTENSION FOR A HUMAN DRUG PRODUCT		
1. Enter the number of days for the testing phase as defined in 37 CFR 1.775(c)(1)	1629	
2. Enter the number of days for the approval phase as defined in 37 CFR 1.775(c)(2)	180	
3. Add line 1 and line 2 and enter the total here	1809	
4. Enter the number of days of the period of line 2 which occurred prior to the issue date of the patent	0	
5. Enter the number of days the period of line 2 during which the applicant failed to act with due diligence as defined in 37 CFR 1.775(d)(1)(ii)	0	
6. Add line 4 and line 5 and enter the total here	0	
7. Subtract line 6 from line 3 and enter the difference here (if less than zero enter 0)	1809	
8. Enter the number of days of the period of line 1 which occurred prior to the issue date of the patent	0	
9. Enter the number of days of the period of line 1 during which the applicant failed to act with due diligence as defined in 37 CFR 1.775(d)(1)(ii)	0	
10. Add line 8 and line 9 and enter the total here	0	
11. Subtract line 10 from line 7 and enter the difference here	1809	
12. Enter the number of days from line 1	1629	
13. Enter the number of days from line 10	0	
14. Subtract line 13 from line 12 and enter the difference here (if less than zero enter 0)	1629	
15. Multiply line 14 by 0.5 (one half) and enter the amount here	814	
16. Subtract line 15 from line 11 and enter the difference here (if less than zero enter 0)	995	
17. Enter the original expiration date of the patent	12.30.14	
18. Enter the expiration date of the patent if extended by the number of days on line 16	09.20.17	
19. Enter the date of the FDA (Food and Drug Administration) final approval	06.15.07	
20. Limitation set forth in 37 CFR 1.775(d)(3)	14 years	
21. Add the number of years on line 20 to the date on line 19 and enter the revised date here	06.15.21	
22. Enter the earlier date appearing on line 18 or line 21	09.20.17	
23. Enter the original expiration date of the patent (from line 17)	12.30.14	
24. Check one of the following three boxes and enter the listed time period here	5 years	
<input checked="" type="checkbox"/>	The patent issued after 24/9/84	5 Years
<input type="checkbox"/>	The patent issued prior to 24/9/84 and no request for exemption as defined in 37 CFR 1.775(d)(6)(i) was filed prior to 24/9/84	5 Years
<input type="checkbox"/>	The patent issued prior to 24/9/84 and an exemption as defined in 37 CFR 1.775(d)(6)(ii) was filed prior to 24/9/84	2 Years
25. Add the number of years on line 24 to the date on line 23 and enter the revised date here	12.30.19	
26. Enter the earlier date appearing on line 22 or line 25	09.20.17	
27. Enter the original expiration date of the patent (from line 17)	12.30.14	
28. Enter the number of days by which line 26 and line 27 differ here This is the length of patent term extension	995	

INFORMATION OBTAINED FROM THE U.S. PATENT AND TRADEMARK OFFICE